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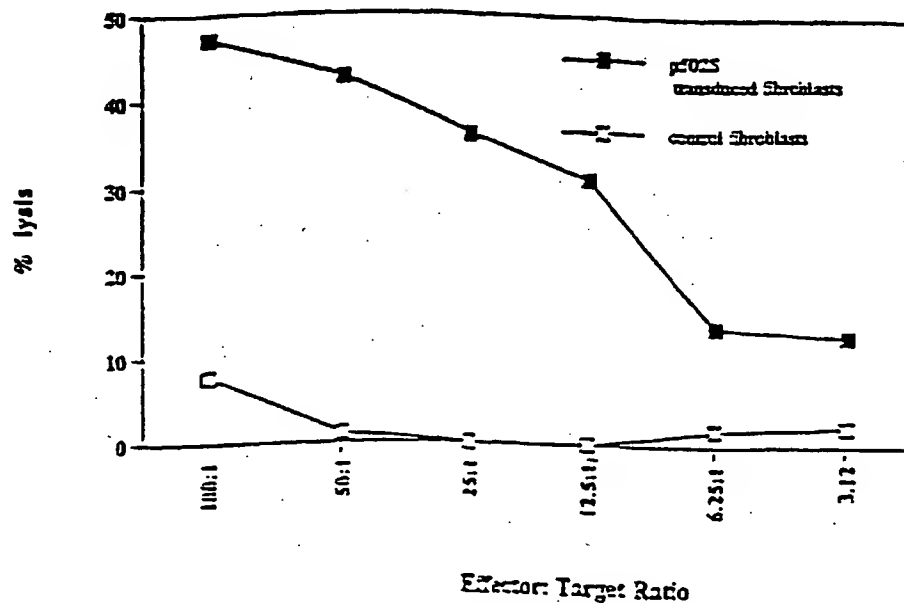
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(54) Title: COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF PROSTATE CANCER



(57) Abstract: Compositions and methods for the therapy and diagnosis of cancer, particularly prostate cancer, are disclosed. Illustrative compositions comprise one or more prostate-specific polypeptides, immunogenic portions thereof, polynucleotides that encode such polypeptides, antigen presenting cell that expresses such polypeptides, and T cells that are specific for cells expressing such polypeptides. The disclosed compositions are useful, for example, in the diagnosis, prevention and/or treatment of diseases, particularly prostate cancer.

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## COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF PROSTATE CANCER

### 5 TECHNICAL FIELD OF THE INVENTION

The present invention relates generally to therapy and diagnosis of cancer, such as prostate cancer. The invention is more specifically related to polypeptides, comprising at least a portion of a prostate-specific protein, and to polynucleotides encoding such polypeptides. Such polypeptides and polynucleotides  
10 are useful in pharmaceutical compositions, *e.g.*, vaccines, and other compositions for the diagnosis and treatment of prostate cancer.

### BACKGROUND OF THE INVENTION

Cancer is a significant health problem throughout the world. Although  
Cancer is a significant health problem throughout the world. Although advances have  
15 been made in detection and therapy of cancer, no vaccine or other universally successful method for prevention or treatment is currently available. Current therapies, which are generally based on a combination of chemotherapy or surgery and radiation, continue to prove inadequate in many patients.

Prostate cancer is the most common form of cancer among males, with  
20 an estimated incidence of 30% in men over the age of 50. Overwhelming clinical evidence shows that human prostate cancer has the propensity to metastasize to bone, and the disease appears to progress inevitably from androgen dependent to androgen refractory status, leading to increased patient mortality. This prevalent disease is currently the second leading cause of cancer death among men in the U.S.

25 In spite of considerable research into therapies for the disease, prostate cancer remains difficult to treat. Commonly, treatment is based on surgery and/or radiation therapy, but these methods are ineffective in a significant percentage of cases. Two previously identified prostate specific proteins - prostate specific antigen (PSA)

and prostatic acid phosphatase (PAP) - have limited therapeutic and diagnostic potential. For example, PSA levels do not always correlate well with the presence of prostate cancer, being positive in a percentage of non-prostate cancer cases, including benign prostatic hyperplasia (BPH). Furthermore, PSA measurements correlate with  
5 prostate volume, and do not indicate the level of metastasis.

In spite of considerable research into therapies for these and other cancers, prostate cancer remains difficult to diagnose and treat effectively. Accordingly, there is a need in the art for improved methods for detecting and treating such cancers. The present invention fulfills these needs and further provides other related advantages.

## 10 SUMMARY OF THE INVENTION

In one aspect, the present invention provides polynucleotide compositions comprising a sequence selected from the group consisting of:

(a) sequences provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524,  
15 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(b) complements of the sequences provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382  
20 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(c) sequences consisting of at least 20 contiguous residues of a sequence provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315,  
25 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(d) sequences that hybridize to a sequence provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375,



381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788, under moderately stringent conditions;

5 (e) sequences having at least 75% identity to a sequence of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

10 (f) sequences having at least 90% identity to a sequence of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788; and

15 (g) degenerate variants of a sequence provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788.

20 In one preferred embodiment, the polynucleotide compositions of the invention are expressed in at least about 20%, more preferably in at least about 30%, and most preferably in at least about 50% of prostate tissue samples tested, at a level that is at least about 2-fold, preferably at least about 5-fold, and most preferably at least about 10-fold higher than that for other normal tissues.

25 The present invention, in another aspect, provides polypeptide compositions comprising an amino acid sequence that is encoded by a polynucleotide sequence described above.

The present invention further provides polypeptide compositions comprising an amino acid sequence selected from the group consisting of sequences  
30 recited in SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383,

477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 and 789-791.

In certain preferred embodiments, the polypeptides and/or  
5 polynucleotides of the present invention are immunogenic, *i.e.*, they are capable of eliciting an immune response, particularly a humoral and/or cellular immune response, as further described herein.

The present invention further provides fragments, variants and/or derivatives of the disclosed polypeptide and/or polynucleotide sequences, wherein the  
10 fragments, variants and/or derivatives preferably have a level of immunogenic activity of at least about 50%, preferably at least about 70% and more preferably at least about 90% of the level of immunogenic activity of a polypeptide sequence set forth in SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-  
15 629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 or 789-791, or a polypeptide sequence encoded by a polynucleotide sequence set forth in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626,  
20 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788.

The present invention further provides polynucleotides that encode a polypeptide described above, expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

25 Within other aspects, the present invention provides pharmaceutical compositions comprising a polypeptide or polynucleotide as described above and a physiologically acceptable carrier.

Within a related aspect of the present invention, pharmaceutical compositions, *e.g.*, vaccine compositions, are provided for prophylactic or therapeutic  
30 applications. Such compositions generally comprise an immunogenic polypeptide or

polynucleotide of the invention and an immunostimulant, such as an adjuvant, together with a physiologically acceptable carrier.

The present invention further provides pharmaceutical compositions that comprise: (a) an antibody or antigen-binding fragment thereof that specifically binds to  
5 a polypeptide of the present invention, or a fragment thereof; and (b) a physiologically acceptable carrier.

Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a pharmaceutically acceptable carrier or excipient. Illustrative  
10 antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B cells.

Within related aspects, pharmaceutical compositions are provided that comprise: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) an immunostimulant.

15 The present invention further provides, in other aspects, fusion proteins that comprise at least one polypeptide as described above, as well as polynucleotides encoding such fusion proteins, typically in the form of pharmaceutical compositions, *e.g.*, vaccine compositions, comprising a physiologically acceptable carrier and/or an immunostimulant. The fusions proteins may comprise multiple immunogenic  
20 polypeptides or portions/variants thereof, as described herein, and may further comprise one or more polypeptide segments for facilitating and/or enhancing the expression, purification and/or immunogenicity of the polypeptide(s).

Within further aspects, the present invention provides methods for stimulating an immune response in a patient, preferably a T cell response in a human  
25 patient, comprising administering a pharmaceutical composition described herein. The patient may be afflicted with prostate cancer, in which case the methods provide treatment for the disease, or a patient considered to be at risk for such a disease may be treated prophylactically.

Within further aspects, the present invention provides methods for  
30 inhibiting the development of a cancer in a patient, comprising administering to a

patient a pharmaceutical composition as recited above. The patient may be afflicted with prostate cancer, in which case the methods provide treatment for the disease, or a patient considered to be at risk for such a disease may be treated prophylactically.

The present invention further provides, within other aspects, methods for  
5 removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a polypeptide of the present invention, wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the polypeptide from the sample.

Within related aspects, methods are provided for inhibiting the  
10 development of a cancer in a patient, comprising administering to a patient a biological sample treated as described above.

Methods are further provided, within other aspects, for stimulating and/or expanding T cells specific for a polypeptide of the present invention, comprising contacting T cells with one or more of: (i) a polypeptide as described above; (ii) a  
15 polynucleotide encoding such a polypeptide; and (iii) an antigen presenting cell that expresses such a polypeptide; under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Isolated T cell populations comprising T cells prepared as described above are also provided.

Within further aspects, the present invention provides methods for  
20 inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population as described above.

The present invention further provides methods for inhibiting the development of a cancer in a patient, comprising the steps of: (a) incubating  $CD4^{+}$  and/or  $CD8^{+}$  T cells isolated from a patient with one or more of: (i) a polypeptide  
25 comprising at least an immunogenic portion of polypeptide disclosed herein; (ii) a polynucleotide encoding such a polypeptide; and (iii) an antigen-presenting cell that expressed such a polypeptide; and (b) administering to the patient an effective amount of the proliferated T cells, thereby inhibiting the development of a cancer in the patient. Proliferated cells may, but need not, be cloned prior to administration to the patient.

Within further aspects, the present invention provides methods for determining the presence or absence of a cancer, preferably a prostate cancer, in a patient comprising: (a) contacting a biological sample obtained from a patient with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and (c) comparing the amount of polypeptide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within preferred embodiments, the binding agent is an antibody, more preferably a monoclonal antibody.

The present invention also provides, within other aspects, methods for monitoring the progression of a cancer in a patient. Such methods comprise the steps of: (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polypeptide detected in step (c) with the amount detected in step (b), and therefrom monitoring the progression of the cancer in the patient.

The present invention further provides, within other aspects, methods for determining the presence or absence of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide of the present invention; (b) detecting in the sample a level of a polynucleotide, preferably mRNA, that hybridizes to the oligonucleotide; and (c) comparing the level of polynucleotide that hybridizes to the oligonucleotide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within certain embodiments, the amount of mRNA is detected via polymerase chain reaction using, for example, at least one oligonucleotide primer that hybridizes to a polynucleotide of the present invention, or a complement of such a polynucleotide. Within other embodiments, the amount of mRNA is detected using a hybridization technique, employing an oligonucleotide probe that hybridizes to an inventive polynucleotide, or a complement of such a polynucleotide.

In related aspects, methods are provided for monitoring the progression of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide of the present invention; (b) detecting in the sample an amount of a polynucleotide that  
5 hybridizes to the oligonucleotide; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polynucleotide detected in step (c) with the amount detected in step (b), and therefrom monitoring the progression of the cancer in the patient.

Within further aspects, the present invention provides antibodies, such as  
10 monoclonal antibodies, that bind to a polypeptide as described above, as well as diagnostic kits comprising such antibodies. Diagnostic kits comprising one or more oligonucleotide probes or primers as described above are also provided.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All  
15 references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

#### BRIEF DESCRIPTION OF THE DRAWINGS AND SEQUENCE IDENTIFIERS

Figure 1 illustrates the ability of T cells to kill fibroblasts expressing the representative prostate-specific polypeptide P502S, as compared to control fibroblasts.  
20 The percentage lysis is shown as a series of effector:target ratios, as indicated.

Figures 2A and 2B illustrate the ability of T cells to recognize cells expressing the representative prostate-specific polypeptide P502S. In each case, the number of  $\gamma$ -interferon spots is shown for different numbers of responders. In Figure 2A, data is presented for fibroblasts pulsed with the P2S-12 peptide, as compared to  
25 fibroblasts pulsed with a control E75 peptide. In Figure 2B, data is presented for fibroblasts expressing P502S, as compared to fibroblasts expressing HER-2/*neu*.

Figure 3 represents a peptide competition binding assay showing that the P1S#10 peptide, derived from P501S, binds HLA-A2. Peptide P1S#10 inhibits HLA-A2 restricted presentation of fluM58 peptide to CTL clone D150M58 in TNF release

bioassay. D150M58 CTL is specific for the HLA-A2 binding influenza matrix peptide fluM58.

Figure 4 illustrates the ability of T cell lines generated from P1S#10 immunized mice to specifically lyse P1S#10-pulsed Jurkat A2Kb targets and P501S-  
5 transduced Jurkat A2Kb targets, as compared to EGFP-transduced Jurkat A2Kb. The percent lysis is shown as a series of effector to target ratios, as indicated.

Figure 5 illustrates the ability of a T cell clone to recognize and specifically lyse Jurkat A2Kb cells expressing the representative prostate-specific polypeptide P501S, thereby demonstrating that the P1S#10 peptide may be a naturally  
10 processed epitope of the P501S polypeptide.

Figures 6A and 6B are graphs illustrating the specificity of a CD8<sup>+</sup> cell line (3A-1) for a representative prostate-specific antigen (P501S). Figure 6A shows the results of a <sup>51</sup>Cr release assay. The percent specific lysis is shown as a series of effector:target ratios, as indicated. Figure 6B shows the production of interferon-  
15 gamma by 3A-1 cells stimulated with autologous B-LCL transduced with P501S, at varying effector:target ratios as indicated.

Figure 7 is a Western blot showing the expression of P501S in baculovirus.

Figure 8 illustrates the results of epitope mapping studies on P501S.

20 Figure 9 is a schematic representation of the P501S protein showing the location of transmembrane domains and predicted intracellular and extracellular domains.

Figure 10 is a genomic map showing the location of the prostate genes P775P, P704P, B305D, P712P and P774P within the Cat Eye Syndrome region of  
25 chromosome 22q11.2

Figure 11 shows the results of an ELISA assay to determine the specificity of rabbit polyclonal antisera raised against P501S.

SEQ ID NO: 1 is the determined cDNA sequence for F1-13

SEQ ID NO: 2 is the determined 3' cDNA sequence for F1-12

30 SEQ ID NO: 3 is the determined 5' cDNA sequence for F1-12

SEQ ID NO: 4 is the determined 3' cDNA sequence for F1-16  
SEQ ID NO: 5 is the determined 3' cDNA sequence for H1-1  
SEQ ID NO: 6 is the determined 3' cDNA sequence for H1-9  
SEQ ID NO: 7 is the determined 3' cDNA sequence for H1-4  
5 SEQ ID NO: 8 is the determined 3' cDNA sequence for J1-17  
SEQ ID NO: 9 is the determined 5' cDNA sequence for J1-17  
SEQ ID NO: 10 is the determined 3' cDNA sequence for L1-12  
SEQ ID NO: 11 is the determined 5' cDNA sequence for L1-12  
SEQ ID NO: 12 is the determined 3' cDNA sequence for N1-1862  
10 SEQ ID NO: 13 is the determined 5' cDNA sequence for N1-1862  
SEQ ID NO: 14 is the determined 3' cDNA sequence for J1-13  
SEQ ID NO: 15 is the determined 5' cDNA sequence for J1-13  
SEQ ID NO: 16 is the determined 3' cDNA sequence for J1-19  
SEQ ID NO: 17 is the determined 5' cDNA sequence for J1-19  
15 SEQ ID NO: 18 is the determined 3' cDNA sequence for J1-25  
SEQ ID NO: 19 is the determined 5' cDNA sequence for J1-25  
SEQ ID NO: 20 is the determined 5' cDNA sequence for J1-24  
SEQ ID NO: 21 is the determined 3' cDNA sequence for J1-24  
SEQ ID NO: 22 is the determined 5' cDNA sequence for K1-58  
20 SEQ ID NO: 23 is the determined 3' cDNA sequence for K1-58  
SEQ ID NO: 24 is the determined 5' cDNA sequence for K1-63  
SEQ ID NO: 25 is the determined 3' cDNA sequence for K1-63  
SEQ ID NO: 26 is the determined 5' cDNA sequence for L1-4  
SEQ ID NO: 27 is the determined 3' cDNA sequence for L1-4  
25 SEQ ID NO: 28 is the determined 5' cDNA sequence for L1-14  
SEQ ID NO: 29 is the determined 3' cDNA sequence for L1-14  
SEQ ID NO: 30 is the determined 3' cDNA sequence for J1-12  
SEQ ID NO: 31 is the determined 3' cDNA sequence for J1-16  
SEQ ID NO: 32 is the determined 3' cDNA sequence for J1-21  
30 SEQ ID NO: 33 is the determined 3' cDNA sequence for K1-48



SEQ ID NO: 34 is the determined 3' cDNA sequence for K1-55  
SEQ ID NO: 35 is the determined 3' cDNA sequence for L1-2  
SEQ ID NO: 36 is the determined 3' cDNA sequence for L1-6  
SEQ ID NO: 37 is the determined 3' cDNA sequence for N1-1858  
5 SEQ ID NO: 38 is the determined 3' cDNA sequence for N1-1860  
SEQ ID NO: 39 is the determined 3' cDNA sequence for N1-1861  
SEQ ID NO: 40 is the determined 3' cDNA sequence for N1-1864  
SEQ ID NO: 41 is the determined cDNA sequence for P5  
SEQ ID NO: 42 is the determined cDNA sequence for P8  
10 SEQ ID NO: 43 is the determined cDNA sequence for P9  
SEQ ID NO: 44 is the determined cDNA sequence for P18  
SEQ ID NO: 45 is the determined cDNA sequence for P20  
SEQ ID NO: 46 is the determined cDNA sequence for P29  
SEQ ID NO: 47 is the determined cDNA sequence for P30  
15 SEQ ID NO: 48 is the determined cDNA sequence for P34  
SEQ ID NO: 49 is the determined cDNA sequence for P36  
SEQ ID NO: 50 is the determined cDNA sequence for P38  
SEQ ID NO: 51 is the determined cDNA sequence for P39  
SEQ ID NO: 52 is the determined cDNA sequence for P42  
20 SEQ ID NO: 53 is the determined cDNA sequence for P47  
SEQ ID NO: 54 is the determined cDNA sequence for P49  
SEQ ID NO: 55 is the determined cDNA sequence for P50  
SEQ ID NO: 56 is the determined cDNA sequence for P53  
SEQ ID NO: 57 is the determined cDNA sequence for P55  
25 SEQ ID NO: 58 is the determined cDNA sequence for P60  
SEQ ID NO: 59 is the determined cDNA sequence for P64  
SEQ ID NO: 60 is the determined cDNA sequence for P65  
SEQ ID NO: 61 is the determined cDNA sequence for P73  
SEQ ID NO: 62 is the determined cDNA sequence for P75  
30 SEQ ID NO: 63 is the determined cDNA sequence for P76

SEQ ID NO: 64 is the determined cDNA sequence for P79  
SEQ ID NO: 65 is the determined cDNA sequence for P84  
SEQ ID NO: 66 is the determined cDNA sequence for P68  
SEQ ID NO: 67 is the determined cDNA sequence for P80 (also referred

5 to as P704P)

SEQ ID NO: 68 is the determined cDNA sequence for P82  
SEQ ID NO: 69 is the determined cDNA sequence for U1-3064  
SEQ ID NO: 70 is the determined cDNA sequence for U1-3065  
SEQ ID NO: 71 is the determined cDNA sequence for V1-3692  
10 SEQ ID NO: 72 is the determined cDNA sequence for 1A-3905  
SEQ ID NO: 73 is the determined cDNA sequence for V1-3686  
SEQ ID NO: 74 is the determined cDNA sequence for R1-2330  
SEQ ID NO: 75 is the determined cDNA sequence for 1B-3976  
SEQ ID NO: 76 is the determined cDNA sequence for V1-3679  
15 SEQ ID NO: 77 is the determined cDNA sequence for 1G-4736  
SEQ ID NO: 78 is the determined cDNA sequence for 1G-4738  
SEQ ID NO: 79 is the determined cDNA sequence for 1G-4741  
SEQ ID NO: 80 is the determined cDNA sequence for 1G-4744  
SEQ ID NO: 81 is the determined cDNA sequence for 1G-4734  
20 SEQ ID NO: 82 is the determined cDNA sequence for 1H-4774  
SEQ ID NO: 83 is the determined cDNA sequence for 1H-4781  
SEQ ID NO: 84 is the determined cDNA sequence for 1H-4785  
SEQ ID NO: 85 is the determined cDNA sequence for 1H-4787  
SEQ ID NO: 86 is the determined cDNA sequence for 1H-4796  
25 SEQ ID NO: 87 is the determined cDNA sequence for 1I-4807  
SEQ ID NO: 88 is the determined cDNA sequence for 1I-4810  
SEQ ID NO: 89 is the determined cDNA sequence for 1I-4811  
SEQ ID NO: 90 is the determined cDNA sequence for 1J-4876  
SEQ ID NO: 91 is the determined cDNA sequence for 1K-4884  
30 SEQ ID NO: 92 is the determined cDNA sequence for 1K-4896

- SEQ ID NO: 93 is the determined cDNA sequence for 1G-4761  
SEQ ID NO: 94 is the determined cDNA sequence for 1G-4762  
SEQ ID NO: 95 is the determined cDNA sequence for 1H-4766  
SEQ ID NO: 96 is the determined cDNA sequence for 1H-4770  
5 SEQ ID NO: 97 is the determined cDNA sequence for 1H-4771  
SEQ ID NO: 98 is the determined cDNA sequence for 1H-4772  
SEQ ID NO: 99 is the determined cDNA sequence for 1D-4297  
SEQ ID NO: 100 is the determined cDNA sequence for 1D-4309  
SEQ ID NO: 101 is the determined cDNA sequence for 1D.1-4278  
10 SEQ ID NO: 102 is the determined cDNA sequence for 1D-4288  
SEQ ID NO: 103 is the determined cDNA sequence for 1D-4283  
SEQ ID NO: 104 is the determined cDNA sequence for 1D-4304  
SEQ ID NO: 105 is the determined cDNA sequence for 1D-4296  
SEQ ID NO: 106 is the determined cDNA sequence for 1D-4280  
15 SEQ ID NO: 107 is the determined full length cDNA sequence for F1-12  
(also referred to as P504S)  
SEQ ID NO: 108 is the predicted amino acid sequence for F1-12  
SEQ ID NO: 109 is the determined full length cDNA sequence for J1-17  
SEQ ID NO: 110 is the determined full length cDNA sequence for L1-12  
20 (also referred to as P501S)  
SEQ ID NO: 111 is the determined full length cDNA sequence for N1-  
1862 (also referred to as P503S)  
SEQ ID NO: 112 is the predicted amino acid sequence for J1-17  
SEQ ID NO: 113 is the predicted amino acid sequence for L1-12 (also  
25 referred to as P501S)  
SEQ ID NO: 114 is the predicted amino acid sequence for N1-1862 (also  
referred to as P503S)  
SEQ ID NO: 115 is the determined cDNA sequence for P89  
SEQ ID NO: 116 is the determined cDNA sequence for P90  
30 SEQ ID NO: 117 is the determined cDNA sequence for P92

SEQ ID NO: 118 is the determined cDNA sequence for P95  
SEQ ID NO: 119 is the determined cDNA sequence for P98  
SEQ ID NO: 120 is the determined cDNA sequence for P102  
SEQ ID NO: 121 is the determined cDNA sequence for P110  
5 SEQ ID NO: 122 is the determined cDNA sequence for P111  
SEQ ID NO: 123 is the determined cDNA sequence for P114  
SEQ ID NO: 124 is the determined cDNA sequence for P115  
SEQ ID NO: 125 is the determined cDNA sequence for P116  
SEQ ID NO: 126 is the determined cDNA sequence for P124  
10 SEQ ID NO: 127 is the determined cDNA sequence for P126  
SEQ ID NO: 128 is the determined cDNA sequence for P130  
SEQ ID NO: 129 is the determined cDNA sequence for P133  
SEQ ID NO: 130 is the determined cDNA sequence for P138  
SEQ ID NO: 131 is the determined cDNA sequence for P143  
15 SEQ ID NO: 132 is the determined cDNA sequence for P151  
SEQ ID NO: 133 is the determined cDNA sequence for P156  
SEQ ID NO: 134 is the determined cDNA sequence for P157  
SEQ ID NO: 135 is the determined cDNA sequence for P166  
SEQ ID NO: 136 is the determined cDNA sequence for P176  
20 SEQ ID NO: 137 is the determined cDNA sequence for P178  
SEQ ID NO: 138 is the determined cDNA sequence for P179  
SEQ ID NO: 139 is the determined cDNA sequence for P185  
SEQ ID NO: 140 is the determined cDNA sequence for P192  
SEQ ID NO: 141 is the determined cDNA sequence for P201  
25 SEQ ID NO: 142 is the determined cDNA sequence for P204  
SEQ ID NO: 143 is the determined cDNA sequence for P208  
SEQ ID NO: 144 is the determined cDNA sequence for P211  
SEQ ID NO: 145 is the determined cDNA sequence for P213  
SEQ ID NO: 146 is the determined cDNA sequence for P219  
30 SEQ ID NO: 147 is the determined cDNA sequence for P237

SEQ ID NO: 148 is the determined cDNA sequence for P239  
SEQ ID NO: 149 is the determined cDNA sequence for P248  
SEQ ID NO: 150 is the determined cDNA sequence for P251  
SEQ ID NO: 151 is the determined cDNA sequence for P255  
5 SEQ ID NO: 152 is the determined cDNA sequence for P256  
SEQ ID NO: 153 is the determined cDNA sequence for P259  
SEQ ID NO: 154 is the determined cDNA sequence for P260  
SEQ ID NO: 155 is the determined cDNA sequence for P263  
SEQ ID NO: 156 is the determined cDNA sequence for P264  
10 SEQ ID NO: 157 is the determined cDNA sequence for P266  
SEQ ID NO: 158 is the determined cDNA sequence for P270  
SEQ ID NO: 159 is the determined cDNA sequence for P272  
SEQ ID NO: 160 is the determined cDNA sequence for P278  
SEQ ID NO: 161 is the determined cDNA sequence for P105  
15 SEQ ID NO: 162 is the determined cDNA sequence for P107  
SEQ ID NO: 163 is the determined cDNA sequence for P137  
SEQ ID NO: 164 is the determined cDNA sequence for P194  
SEQ ID NO: 165 is the determined cDNA sequence for P195  
SEQ ID NO: 166 is the determined cDNA sequence for P196  
20 SEQ ID NO: 167 is the determined cDNA sequence for P220  
SEQ ID NO: 168 is the determined cDNA sequence for P234  
SEQ ID NO: 169 is the determined cDNA sequence for P235  
SEQ ID NO: 170 is the determined cDNA sequence for P243  
SEQ ID NO: 171 is the determined cDNA sequence for P703P-DE1  
25 SEQ ID NO: 172 is the predicted amino acid sequence for P703P-DE1  
SEQ ID NO: 173 is the determined cDNA sequence for P703P-DE2  
SEQ ID NO: 174 is the determined cDNA sequence for P703P-DE6  
SEQ ID NO: 175 is the determined cDNA sequence for P703P-DE13  
SEQ ID NO: 176 is the predicted amino acid sequence for P703P-DE13  
30 SEQ ID NO: 177 is the determined cDNA sequence for P703P-DE14

SEQ ID NO: 178 is the predicted amino acid sequence for P703P-DE14

SEQ ID NO: 179 is the determined extended cDNA sequence for 1G-

4736

SEQ ID NO: 180 is the determined extended cDNA sequence for 1G-

5 4738

SEQ ID NO: 181 is the determined extended cDNA sequence for 1G-

4741

SEQ ID NO: 182 is the determined extended cDNA sequence for 1G-

4744

10

SEQ ID NO: 183 is the determined extended cDNA sequence for 1H-

4774

SEQ ID NO: 184 is the determined extended cDNA sequence for 1H-

4781

SEQ ID NO: 185 is the determined extended cDNA sequence for 1H-

15 4785

SEQ ID NO: 186 is the determined extended cDNA sequence for 1H-

4787

SEQ ID NO: 187 is the determined extended cDNA sequence for 1H-

4796

20

SEQ ID NO: 188 is the determined extended cDNA sequence for 1I-

4807

SEQ ID NO: 189 is the determined 3' cDNA sequence for 1I-4810

SEQ ID NO: 190 is the determined 3' cDNA sequence for 1I-4811

SEQ ID NO: 191 is the determined extended cDNA sequence for 1J-

25 4876

SEQ ID NO: 192 is the determined extended cDNA sequence for 1K-

4884

SEQ ID NO: 193 is the determined extended cDNA sequence for 1K-

4896

SEQ ID NO: 194 is the determined extended cDNA sequence for 1G-  
4761

SEQ ID NO: 195 is the determined extended cDNA sequence for 1G-  
4762

5 SEQ ID NO: 196 is the determined extended cDNA sequence for 1H-  
4766

SEQ ID NO: 197 is the determined 3' cDNA sequence for 1H-4770  
SEQ ID NO: 198 is the determined 3' cDNA sequence for 1H-4771  
SEQ ID NO: 199 is the determined extended cDNA sequence for 1H-  
10 4772

SEQ ID NO: 200 is the determined extended cDNA sequence for 1D-  
4309

SEQ ID NO: 201 is the determined extended cDNA sequence for 1D.1-  
4278

15 SEQ ID NO: 202 is the determined extended cDNA sequence for 1D-  
4288

SEQ ID NO: 203 is the determined extended cDNA sequence for 1D-  
4283

SEQ ID NO: 204 is the determined extended cDNA sequence for 1D-  
20 4304

SEQ ID NO: 205 is the determined extended cDNA sequence for 1D-  
4296

SEQ ID NO: 206 is the determined extended cDNA sequence for 1D-  
4280

25 SEQ ID NO: 207 is the determined cDNA sequence for 10-d8fwd  
SEQ ID NO: 208 is the determined cDNA sequence for 10-H10con  
SEQ ID NO: 209 is the determined cDNA sequence for 11-C8rev  
SEQ ID NO: 210 is the determined cDNA sequence for 7.g6fwd  
SEQ ID NO: 211 is the determined cDNA sequence for 7.g6rev  
30 SEQ ID NO: 212 is the determined cDNA sequence for 8-b5fwd

SEQ ID NO: 213 is the determined cDNA sequence for 8-b5rev  
SEQ ID NO: 214 is the determined cDNA sequence for 8-b6fwd  
SEQ ID NO: 215 is the determined cDNA sequence for 8-b6 rev  
SEQ ID NO: 216 is the determined cDNA sequence for 8-d4fwd  
5 SEQ ID NO: 217 is the determined cDNA sequence for 8-d9rev  
SEQ ID NO: 218 is the determined cDNA sequence for 8-g3fwd  
SEQ ID NO: 219 is the determined cDNA sequence for 8-g3rev  
SEQ ID NO: 220 is the determined cDNA sequence for 8-h11rev  
SEQ ID NO: 221 is the determined cDNA sequence for g-f12fwd  
10 SEQ ID NO: 222 is the determined cDNA sequence for g-f3rev  
SEQ ID NO: 223 is the determined cDNA sequence for P509S  
SEQ ID NO: 224 is the determined cDNA sequence for P510S  
SEQ ID NO: 225 is the determined cDNA sequence for P703DE5  
SEQ ID NO: 226 is the determined cDNA sequence for 9-A11  
15 SEQ ID NO: 227 is the determined cDNA sequence for 8-C6  
SEQ ID NO: 228 is the determined cDNA sequence for 8-H7  
SEQ ID NO: 229 is the determined cDNA sequence for JPTPN13  
SEQ ID NO: 230 is the determined cDNA sequence for JPTPN14  
SEQ ID NO: 231 is the determined cDNA sequence for JPTPN23  
20 SEQ ID NO: 232 is the determined cDNA sequence for JPTPN24  
SEQ ID NO: 233 is the determined cDNA sequence for JPTPN25  
SEQ ID NO: 234 is the determined cDNA sequence for JPTPN30  
SEQ ID NO: 235 is the determined cDNA sequence for JPTPN34  
SEQ ID NO: 236 is the determined cDNA sequence for PTPN35  
25 SEQ ID NO: 237 is the determined cDNA sequence for JPTPN36  
SEQ ID NO: 238 is the determined cDNA sequence for JPTPN38  
SEQ ID NO: 239 is the determined cDNA sequence for JPTPN39  
SEQ ID NO: 240 is the determined cDNA sequence for JPTPN40  
SEQ ID NO: 241 is the determined cDNA sequence for JPTPN41  
30 SEQ ID NO: 242 is the determined cDNA sequence for JPTPN42



SEQ ID NO: 243 is the determined cDNA sequence for JPTPN45  
SEQ ID NO: 244 is the determined cDNA sequence for JPTPN46  
SEQ ID NO: 245 is the determined cDNA sequence for JPTPN51  
SEQ ID NO: 246 is the determined cDNA sequence for JPTPN56  
5 SEQ ID NO: 247 is the determined cDNA sequence for PTPN64  
SEQ ID NO: 248 is the determined cDNA sequence for JPTPN65  
SEQ ID NO: 249 is the determined cDNA sequence for JPTPN67  
SEQ ID NO: 250 is the determined cDNA sequence for JPTPN76  
SEQ ID NO: 251 is the determined cDNA sequence for JPTPN84  
10 SEQ ID NO: 252 is the determined cDNA sequence for JPTPN85  
SEQ ID NO: 253 is the determined cDNA sequence for JPTPN86  
SEQ ID NO: 254 is the determined cDNA sequence for JPTPN87  
SEQ ID NO: 255 is the determined cDNA sequence for JPTPN88  
SEQ ID NO: 256 is the determined cDNA sequence for JP1F1  
15 SEQ ID NO: 257 is the determined cDNA sequence for JP1F2  
SEQ ID NO: 258 is the determined cDNA sequence for JP1C2  
SEQ ID NO: 259 is the determined cDNA sequence for JP1B1  
SEQ ID NO: 260 is the determined cDNA sequence for JP1B2  
SEQ ID NO: 261 is the determined cDNA sequence for JP1D3  
20 SEQ ID NO: 262 is the determined cDNA sequence for JP1A4  
SEQ ID NO: 263 is the determined cDNA sequence for JP1F5  
SEQ ID NO: 264 is the determined cDNA sequence for JP1E6  
SEQ ID NO: 265 is the determined cDNA sequence for JP1D6  
SEQ ID NO: 266 is the determined cDNA sequence for JP1B5  
25 SEQ ID NO: 267 is the determined cDNA sequence for JP1A6  
SEQ ID NO: 268 is the determined cDNA sequence for JP1E8  
SEQ ID NO: 269 is the determined cDNA sequence for JP1D7  
SEQ ID NO: 270 is the determined cDNA sequence for JP1D9  
SEQ ID NO: 271 is the determined cDNA sequence for JP1C10  
30 SEQ ID NO: 272 is the determined cDNA sequence for JP1A9

SEQ ID NO: 273 is the determined cDNA sequence for JP1F12  
SEQ ID NO: 274 is the determined cDNA sequence for JP1E12  
SEQ ID NO: 275 is the determined cDNA sequence for JP1D11  
SEQ ID NO: 276 is the determined cDNA sequence for JP1C11  
5 SEQ ID NO: 277 is the determined cDNA sequence for JP1C12  
SEQ ID NO: 278 is the determined cDNA sequence for JP1B12  
SEQ ID NO: 279 is the determined cDNA sequence for JP1A12  
SEQ ID NO: 280 is the determined cDNA sequence for JP8G2  
SEQ ID NO: 281 is the determined cDNA sequence for JP8H1  
10 SEQ ID NO: 282 is the determined cDNA sequence for JP8H2  
SEQ ID NO: 283 is the determined cDNA sequence for JP8A3  
SEQ ID NO: 284 is the determined cDNA sequence for JP8A4  
SEQ ID NO: 285 is the determined cDNA sequence for JP8C3  
SEQ ID NO: 286 is the determined cDNA sequence for JP8G4  
15 SEQ ID NO: 287 is the determined cDNA sequence for JP8B6  
SEQ ID NO: 288 is the determined cDNA sequence for JP8D6  
SEQ ID NO: 289 is the determined cDNA sequence for JP8F5  
SEQ ID NO: 290 is the determined cDNA sequence for JP8A8  
SEQ ID NO: 291 is the determined cDNA sequence for JP8C7  
20 SEQ ID NO: 292 is the determined cDNA sequence for JP8D7  
SEQ ID NO: 293 is the determined cDNA sequence for P8D8  
SEQ ID NO: 294 is the determined cDNA sequence for JP8E7  
SEQ ID NO: 295 is the determined cDNA sequence for JP8F8  
SEQ ID NO: 296 is the determined cDNA sequence for JP8G8  
25 SEQ ID NO: 297 is the determined cDNA sequence for JP8B10  
SEQ ID NO: 298 is the determined cDNA sequence for JP8C10  
SEQ ID NO: 299 is the determined cDNA sequence for JP8E9  
SEQ ID NO: 300 is the determined cDNA sequence for JP8E10  
SEQ ID NO: 301 is the determined cDNA sequence for JP8F9  
30 SEQ ID NO: 302 is the determined cDNA sequence for JP8H9

- SEQ ID NO: 303 is the determined cDNA sequence for JP8C12  
SEQ ID NO: 304 is the determined cDNA sequence for JP8E11  
SEQ ID NO: 305 is the determined cDNA sequence for JP8E12  
SEQ ID NO: 306 is the amino acid sequence for the peptide PS2#12  
5 SEQ ID NO: 307 is the determined cDNA sequence for P711P  
SEQ ID NO: 308 is the determined cDNA sequence for P712P  
SEQ ID NO: 309 is the determined cDNA sequence for CLONE23  
SEQ ID NO: 310 is the determined cDNA sequence for P774P  
SEQ ID NO: 311 is the determined cDNA sequence for P775P  
10 SEQ ID NO: 312 is the determined cDNA sequence for P715P  
SEQ ID NO: 313 is the determined cDNA sequence for P710P  
SEQ ID NO: 314 is the determined cDNA sequence for P767P  
SEQ ID NO: 315 is the determined cDNA sequence for P768P  
SEQ ID NO: 316-325 are the determined cDNA sequences of previously  
15 isolated genes  
SEQ ID NO: 326 is the determined cDNA sequence for P703PDE5  
SEQ ID NO: 327 is the predicted amino acid sequence for P703PDE5  
SEQ ID NO: 328 is the determined cDNA sequence for P703P6.26  
SEQ ID NO: 329 is the predicted amino acid sequence for P703P6.26  
20 SEQ ID NO: 330 is the determined cDNA sequence for P703PX-23  
SEQ ID NO: 331 is the predicted amino acid sequence for P703PX-23  
SEQ ID NO: 332 is the determined full length cDNA sequence for  
P509S  
SEQ ID NO: 333 is the determined extended cDNA sequence for P707P  
25 (also referred to as 11-C9)  
SEQ ID NO: 334 is the determined cDNA sequence for P714P  
SEQ ID NO: 335 is the determined cDNA sequence for P705P (also  
referred to as 9-F3)  
SEQ ID NO: 336 is the predicted amino acid sequence for P705P  
30 SEQ ID NO: 337 is the amino acid sequence of the peptide P1S#10

- SEQ ID NO: 338 is the amino acid sequence of the peptide p5  
SEQ ID NO: 339 is the predicted amino acid sequence of P509S  
SEQ ID NO: 340 is the determined cDNA sequence for P778P  
SEQ ID NO: 341 is the determined cDNA sequence for P786P  
5 SEQ ID NO: 342 is the determined cDNA sequence for P789P  
SEQ ID NO: 343 is the determined cDNA sequence for a clone showing  
homology to Homo sapiens MM46 mRNA  
SEQ ID NO: 344 is the determined cDNA sequence for a clone showing  
homology to Homo sapiens TNF-alpha stimulated ABC protein (ABC50) mRNA  
10 SEQ ID NO: 345 is the determined cDNA sequence for a clone showing  
homology to Homo sapiens mRNA for E-cadherin  
SEQ ID NO: 346 is the determined cDNA sequence for a clone showing  
homology to Human nuclear-encoded mitochondrial serine hydroxymethyltransferase  
(SHMT)  
15 SEQ ID NO: 347 is the determined cDNA sequence for a clone showing  
homology to Homo sapiens natural resistance-associated macrophage protein2  
(NRAMP2)  
SEQ ID NO: 348 is the determined cDNA sequence for a clone showing  
homology to Homo sapiens phosphoglucomutase-related protein (PGMRP)  
20 SEQ ID NO: 349 is the determined cDNA sequence for a clone showing  
homology to Human mRNA for proteosome subunit p40  
SEQ ID NO: 350 is the determined cDNA sequence for P777P  
SEQ ID NO: 351 is the determined cDNA sequence for P779P  
SEQ ID NO: 352 is the determined cDNA sequence for P790P  
25 SEQ ID NO: 353 is the determined cDNA sequence for P784P  
SEQ ID NO: 354 is the determined cDNA sequence for P776P  
SEQ ID NO: 355 is the determined cDNA sequence for P780P  
SEQ ID NO: 356 is the determined cDNA sequence for P544S  
SEQ ID NO: 357 is the determined cDNA sequence for P745S  
30 SEQ ID NO: 358 is the determined cDNA sequence for P782P

- SEQ ID NO: 359 is the determined cDNA sequence for P783P
- SEQ ID NO: 360 is the determined cDNA sequence for unknown 17984
- SEQ ID NO: 361 is the determined cDNA sequence for P787P
- SEQ ID NO: 362 is the determined cDNA sequence for P788P
- 5 SEQ ID NO: 363 is the determined cDNA sequence for unknown 17994
- SEQ ID NO: 364 is the determined cDNA sequence for P781P
- SEQ ID NO: 365 is the determined cDNA sequence for P785P
- SEQ ID NO: 366-375 are the determined cDNA sequences for splice variants of B305D.
- 10 SEQ ID NO: 376 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 366.
- SEQ ID NO: 377 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 372.
- SEQ ID NO: 378 is the predicted amino acid sequence encoded by the
- 15 sequence of SEQ ID NO: 373.
- SEQ ID NO: 379 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 374.
- SEQ ID NO: 380 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: 375.
- 20 SEQ ID NO: 381 is the determined cDNA sequence for B716P.
- SEQ ID NO: 382 is the determined full-length cDNA sequence for P711P.
- SEQ ID NO: 383 is the predicted amino acid sequence for P711P.
- SEQ ID NO: 384 is the cDNA sequence for P1000C.
- 25 SEQ ID NO: 385 is the cDNA sequence for CGI-82.
- SEQ ID NO: 386 is the cDNA sequence for 23320.
- SEQ ID NO: 387 is the cDNA sequence for CGI-69.
- SEQ ID NO: 388 is the cDNA sequence for L-iditol-2-dehydrogenase.
- SEQ ID NO: 389 is the cDNA sequence for 23379.
- 30 SEQ ID NO: 390 is the cDNA sequence for 23381.

SEQ ID NO:391 is the cDNA sequence for KIAA0122.

SEQ ID NO:392 is the cDNA sequence for 23399.

SEQ ID NO:393 is the cDNA sequence for a previously identified gene.

SEQ ID NO:394 is the cDNA sequence for HCLBP.

5 SEQ ID NO:395 is the cDNA sequence for transglutaminase.

SEQ ID NO:396 is the cDNA sequence for a previously identified gene.

SEQ ID NO:397 is the cDNA sequence for PAP.

SEQ ID NO:398 is the cDNA sequence for Ets transcription factor

PDEF.

10 SEQ ID NO:399 is the cDNA sequence for hTGR.

SEQ ID NO:400 is the cDNA sequence for KIAA0295.

SEQ ID NO:401 is the cDNA sequence for 22545.

SEQ ID NO:402 is the cDNA sequence for 22547.

SEQ ID NO:403 is the cDNA sequence for 22548.

15 SEQ ID NO:404 is the cDNA sequence for 22550.

SEQ ID NO:405 is the cDNA sequence for 22551.

SEQ ID NO:406 is the cDNA sequence for 22552.

SEQ ID NO:407 is the cDNA sequence for 22553 (also known as

P1020C).

20 SEQ ID NO:408 is the cDNA sequence for 22558.

SEQ ID NO:409 is the cDNA sequence for 22562.

SEQ ID NO:410 is the cDNA sequence for 22565.

SEQ ID NO:411 is the cDNA sequence for 22567.

SEQ ID NO:412 is the cDNA sequence for 22568.

25 SEQ ID NO:413 is the cDNA sequence for 22570.

SEQ ID NO:414 is the cDNA sequence for 22571.

SEQ ID NO:415 is the cDNA sequence for 22572.

SEQ ID NO:416 is the cDNA sequence for 22573.

SEQ ID NO:417 is the cDNA sequence for 22573.

30 SEQ ID NO:418 is the cDNA sequence for 22575.

SEQ ID NO:419 is the cDNA sequence for 22580.  
SEQ ID NO:420 is the cDNA sequence for 22581.  
SEQ ID NO:421 is the cDNA sequence for 22582.  
SEQ ID NO:422 is the cDNA sequence for 22583.  
5 SEQ ID NO:423 is the cDNA sequence for 22584.  
SEQ ID NO:424 is the cDNA sequence for 22585.  
SEQ ID NO:425 is the cDNA sequence for 22586.  
SEQ ID NO:426 is the cDNA sequence for 22587.  
SEQ ID NO:427 is the cDNA sequence for 22588.  
10 SEQ ID NO:428 is the cDNA sequence for 22589.  
SEQ ID NO:429 is the cDNA sequence for 22590.  
SEQ ID NO:430 is the cDNA sequence for 22591.  
SEQ ID NO:431 is the cDNA sequence for 22592.  
SEQ ID NO:432 is the cDNA sequence for 22593.  
15 SEQ ID NO:433 is the cDNA sequence for 22594.  
SEQ ID NO:434 is the cDNA sequence for 22595.  
SEQ ID NO:435 is the cDNA sequence for 22596.  
SEQ ID NO:436 is the cDNA sequence for 22847.  
SEQ ID NO:437 is the cDNA sequence for 22848.  
20 SEQ ID NO:438 is the cDNA sequence for 22849.  
SEQ ID NO:439 is the cDNA sequence for 22851.  
SEQ ID NO:440 is the cDNA sequence for 22852.  
SEQ ID NO:441 is the cDNA sequence for 22853.  
SEQ ID NO:442 is the cDNA sequence for 22854.  
25 SEQ ID NO:443 is the cDNA sequence for 22855.  
SEQ ID NO:444 is the cDNA sequence for 22856.  
SEQ ID NO:445 is the cDNA sequence for 22857.  
SEQ ID NO:446 is the cDNA sequence for 23601.  
SEQ ID NO:447 is the cDNA sequence for 23602.  
30 SEQ ID NO:448 is the cDNA sequence for 23605.

- SEQ ID NO:449 is the cDNA sequence for 23606.  
SEQ ID NO:450 is the cDNA sequence for 23612.  
SEQ ID NO:451 is the cDNA sequence for 23614.  
SEQ ID NO:452 is the cDNA sequence for 23618.  
5 SEQ ID NO:453 is the cDNA sequence for 23622.  
SEQ ID NO:454 is the cDNA sequence for folate hydrolase.  
SEQ ID NO:455 is the cDNA sequence for LIM protein.  
SEQ ID NO:456 is the cDNA sequence for a known gene.  
SEQ ID NO:457 is the cDNA sequence for a known gene.  
10 SEQ ID NO:458 is the cDNA sequence for a previously identified gene.  
SEQ ID NO:459 is the cDNA sequence for 23045.  
SEQ ID NO:460 is the cDNA sequence for 23032.  
SEQ ID NO:461 is the cDNA sequence for clone 23054.  
SEQ ID NO:462-467 are cDNA sequences for known genes.  
15 SEQ ID NO:468-471 are cDNA sequences for P710P.  
SEQ ID NO:472 is a cDNA sequence for P1001C.  
SEQ ID NO: 473 is the determined cDNA sequence for a first splice  
variant of P775P (referred to as 27505).  
SEQ ID NO: 474 is the determined cDNA sequence for a second splice  
20 variant of P775P (referred to as 19947).  
SEQ ID NO: 475 is the determined cDNA sequence for a third splice  
variant of P775P (referred to as 19941).  
SEQ ID NO: 476 is the determined cDNA sequence for a fourth splice  
variant of P775P (referred to as 19937).  
25 SEQ ID NO: 477 is a first predicted amino acid sequence encoded by the  
sequence of SEQ ID NO: 474.  
SEQ ID NO: 478 is a second predicted amino acid sequence encoded by  
the sequence of SEQ ID NO: 474.  
SEQ ID NO: 479 is the predicted amino acid sequence encoded by the  
30 sequence of SEQ ID NO: 475.



SEQ ID NO: 480 is a first predicted amino acid sequence encoded by the sequence of SEQ ID NO: 473.

SEQ ID NO: 481 is a second predicted amino acid sequence encoded by the sequence of SEQ ID NO: 473.

5           SEQ ID NO: 482 is a third predicted amino acid sequence encoded by the sequence of SEQ ID NO: 473.

SEQ ID NO: 483 is a fourth predicted amino acid sequence encoded by the sequence of SEQ ID NO: 473.

10           SEQ ID NO: 484 is the first 30 amino acids of the *M. tuberculosis* antigen Ra12.

SEQ ID NO: 485 is the PCR primer AW025.

SEQ ID NO: 486 is the PCR primer AW003.

SEQ ID NO: 487 is the PCR primer AW027.

SEQ ID NO: 488 is the PCR primer AW026.

15           SEQ ID NO: 489-501 are peptides employed in epitope mapping studies.

SEQ ID NO: 502 is the determined cDNA sequence of the complementarity determining region for the anti-P503S monoclonal antibody 20D4.

SEQ ID NO: 503 is the determined cDNA sequence of the complementarity determining region for the anti-P503S monoclonal antibody JA1.

20           SEQ ID NO: 504 & 505 are peptides employed in epitope mapping studies.

SEQ ID NO: 506 is the determined cDNA sequence of the complementarity determining region for the anti-P703P monoclonal antibody 8H2.

25           SEQ ID NO: 507 is the determined cDNA sequence of the complementarity determining region for the anti-P703P monoclonal antibody 7H8.

SEQ ID NO: 508 is the determined cDNA sequence of the complementarity determining region for the anti-P703P monoclonal antibody 2D4.

SEQ ID NO: 509-522 are peptides employed in epitope mapping studies.

30           SEQ ID NO: 523 is a mature form of P703P used to raise antibodies against P703P.

SEQ ID NO: 524 is the putative full-length cDNA sequence of P703P.

SEQ ID NO: 525 is the predicted amino acid sequence encoded by SEQ  
ID NO: 524.

SEQ ID NO: 526 is the full-length cDNA sequence for P790P.

5 SEQ ID NO: 527 is the predicted amino acid sequence for P790P.

SEQ ID NO: 528 & 529 are PCR primers.

SEQ ID NO: 530 is the cDNA sequence of a splice variant of SEQ ID  
NO: 366.

10 SEQ ID NO: 531 is the cDNA sequence of the open reading frame of  
SEQ ID NO: 530.

SEQ ID NO: 532 is the predicted amino acid encoded by the sequence of  
SEQ ID NO: 531.

SEQ ID NO: 533 is the DNA sequence of a putative ORF of P775P.

15 SEQ ID NO: 534 is the predicted amino acid sequence encoded by SEQ  
ID NO: 533.

SEQ ID NO: 535 is a first full-length cDNA sequence for P510S.

SEQ ID NO: 536 is a second full-length cDNA sequence for P510S.

SEQ ID NO: 537 is the predicted amino acid sequence encoded by SEQ  
ID NO: 535.

20 SEQ ID NO: 538 is the predicted amino acid sequence encoded by SEQ  
ID NO: 536.

SEQ ID NO: 539 is the peptide P501S-370.

SEQ ID NO: 540 is the peptide P501S-376.

SEQ ID NO: 541-551 are epitopes of P501S.

25 SEQ ID NO: 552 is an extended cDNA sequence for P712P.

SEQ ID NO: 553-568 are the amino acid sequences encoded by  
predicted open reading frames within SEQ ID NO: 552.

SEQ ID NO: 569 is an extended cDNA sequence for P776P.

30 SEQ ID NO: 570 is the determined cDNA sequence for a splice variant  
of P776P referred to as contig 6.

SEQ ID NO: 571 is the determined cDNA sequence for a splice variant of P776P referred to as contig 7.

SEQ ID NO: 572 is the determined cDNA sequence for a splice variant of P776P referred to as contig 14.

5 SEQ ID NO: 573 is the amino acid sequence encoded by a first predicted ORF of SEQ ID NO: 570.

SEQ ID NO: 574 is the amino acid sequence encoded by a second predicted ORF of SEQ ID NO: 570.

10 SEQ ID NO: 575 is the amino acid sequence encoded by a predicted ORF of SEQ ID NO: 571.

SEQ ID NO: 576-586 are amino acid sequences encoded by predicted ORFs of SEQ ID NO: 569.

SEQ ID NO: 587 is a DNA consensus sequence of the sequences of P767P and P777P.

15 SEQ ID NO: 588-590 are amino acid sequences encoded by predicted ORFs of SEQ ID NO: 587.

SEQ ID NO: 591 is an extended cDNA sequence for P1020C.

SEQ ID NO: 592 is the predicted amino acid sequence encoded by the sequence of SEQ ID NO: P1020C.

20 SEQ ID NO: 593 is a splice variant of P775P referred to as 50748.

SEQ ID NO: 594 is a splice variant of P775P referred to as 50717.

SEQ ID NO: 595 is a splice variant of P775P referred to as 45985.

SEQ ID NO: 596 is a splice variant of P775P referred to as 38769.

SEQ ID NO: 597 is a splice variant of P775P referred to as 37922.

25 SEQ ID NO: 598 is a splice variant of P510S referred to as 49274.

SEQ ID NO: 599 is a splice variant of P510S referred to as 39487.

SEQ ID NO: 600 is a splice variant of P504S referred to as 5167.16.

SEQ ID NO: 601 is a splice variant of P504S referred to as 5167.1.

SEQ ID NO: 602 is a splice variant of P504S referred to as 5163.46.

30 SEQ ID NO: 603 is a splice variant of P504S referred to as 5163.42.

SEQ ID NO: 604 is a splice variant of P504S referred to as 5163.34.

SEQ ID NO: 605 is a splice variant of P504S referred to as 5163.17.

SEQ ID NO: 606 is a splice variant of P501S referred to as 10640.

SEQ ID NO: 607-615 are the sequences of PCR primers.

5       SEQ ID NO: 616 is the determined cDNA sequence of a fusion of P703P  
and PSA.

SEQ ID NO: 617 is the amino acid sequence of the fusion of P703P and  
PSA.

SEQ ID NO: 618 is the cDNA sequence of the gene DD3.

10       SEQ ID NO: 619 is an extended cDNA sequence for P714P.

SEQ ID NO: 620-622 are the cDNA sequences for splice variants of  
P704P.

SEQ ID NO: 623 is the cDNA sequence of a splice variant of P553S  
referred to as P553S-14.

15       SEQ ID NO: 624 is the cDNA sequence of a splice variant of P553S  
referred to as P553S-12.

SEQ ID NO: 625 is the cDNA sequence of a splice variant of P553S  
referred to as P553S-10.

20       SEQ ID NO: 626 is the cDNA sequence of a splice variant of P553S  
referred to as P553S-6.

SEQ ID NO: 627 is the amino acid sequence encoded by SEQ ID NO:  
626.

SEQ ID NO: 628 is a first amino acid sequence encoded by SEQ ID NO:  
623.

25       SEQ ID NO: 629 is a second amino acid sequence encoded by SEQ ID  
NO: 623.

SEQ ID NO: 630 is a first full-length cDNA sequence for prostate-  
specific transglutaminase gene (also referred to herein as P558S).

30       SEQ ID NO: 631 is a second full-length cDNA sequence for prostate-  
specific transglutaminase gene.

SEQ ID NO: 632 is the amino acid sequence encoded by the sequence of  
SEQ ID NO: 630.

SEQ ID NO: 633 is the amino acid sequence encoded by the sequence of  
SEQ ID NO: 631.

5 SEQ ID NO: 634 is the full-length cDNA sequence for P788P.

SEQ ID NO: 635 is the amino acid sequence encoded by SEQ ID NO:  
634.

SEQ ID NO: 636 is the determined cDNA sequence for a polymorphic  
variant of P788P.

10 SEQ ID NO: 637 is the amino acid sequence encoded by SEQ ID NO:  
636.

SEQ ID NO: 638 is the amino acid sequence of peptide 4 from P703P.

SEQ ID NO: 639 is the cDNA sequence that encodes peptide 4 from  
P703P.

15 SEQ ID NO: 640-655 are cDNA sequences encoding epitopes of P703P.

SEQ ID NO: 656-671 are the amino acid sequences of epitopes of  
P703P.

SEQ ID NO: 672 and 673 are PCR primers.

20 SEQ ID NO: 674 is the cDNA sequence encoding an N-terminal portion  
of P788P expressed in *E. coli*.

SEQ ID NO: 675 is the amino acid sequence of the N-terminal portion of  
P788P expressed in *E. coli*.

SEQ ID NO: 676 is the amino acid sequence of the *M. tuberculosis*  
antigen Ra12.

25 SEQ ID NO: 677 and 678 are PCR primers.

SEQ ID NO: 679 is the cDNA sequence for the Ra12-P510S-C  
construct.

SEQ ID NO: 680 is the cDNA sequence for the P510S-C construct.

SEQ ID NO: 681 is the cDNA sequence for the P510S-E3 construct.

SEQ ID NO: 682 is the amino acid sequence for the Ra12-P510S-C construct.

SEQ ID NO: 683 is the amino acid sequence for the P510S-C construct.

SEQ ID NO: 684 is the amino acid sequence for the P510S-E3 construct.

5       SEQ ID NO: 685-690 are PCR primers.

SEQ ID NO: 691 is the cDNA sequence of the construct Ra12-P775P-ORF3.

SEQ ID NO: 692 is the amino acid sequence of the construct Ra12-P775P-ORF3.

10       SEQ ID NO: 693 and 694 are PCR primers.

SEQ ID NO: 695 is the determined amino acid sequence for a P703P His tag fusion protein.

SEQ ID NO: 696 is the determined cDNA sequence for a P703P His tag fusion protein.

15       SEQ ID NO: 697 and 698 are PCR primers.

SEQ ID NO: 699 is the determined amino acid sequence for a P705P His tag fusion protein.

SEQ ID NO: 700 is the determined cDNA sequence for a P705P His tag fusion protein.

20       SEQ ID NO: 701 and 702 are PCR primers.

SEQ ID NO: 703 is the determined amino acid sequence for a P711P His tag fusion protein.

SEQ ID NO: 704 is the determined cDNA sequence for a P711P His tag fusion protein.

25       SEQ ID NO: 705 is the amino acid sequence of the *M. tuberculosis* antigen Ra12.

SEQ ID NO: 706 and 707 are PCR primers.

SEQ ID NO: 708 is the determined cDNA sequence for the construct Ra12-P501S-E2.

SEQ ID NO: 709 is the determined amino acid sequence for the construct Ra12-P501S-E2.

SEQ ID NO: 710 is the amino acid sequence for an epitope of P501S.

SEQ ID NO: 711 is the DNA sequence encoding SEQ ID NO: 710.

5 SEQ ID NO: 712 is the amino acid sequence for an epitope of P501S.

SEQ ID NO: 713 is the DNA sequence encoding SEQ ID NO: 712.

SEQ ID NO: 714 is a peptide employed in epitope mapping studies.

SEQ ID NO: 715 is the amino acid sequence for an epitope of P501S.

SEQ ID NO: 716 is the DNA sequence encoding SEQ ID NO: 715.

10 SEQ ID NO: 717-719 are the amino acid sequences for CD4 epitopes of P501S.

SEQ ID NO: 720-722 are the DNA sequences encoding the sequences of SEQ ID NO: 717-719.

15 SEQ ID NO: 723-734 are the amino acid sequences for putative CTL epitopes of P703P.

SEQ ID NO: 735 is the full-length cDNA sequence for P789P.

SEQ ID NO: 736 is the amino acid sequence encoded by SEQ ID NO: 735.

20 SEQ ID NO: 737 is the determined full-length cDNA sequence for the splice variant of P776P referred to as contig 6.

SEQ ID NO: 738-739 are determined full-length cDNA sequences for the splice variant of P776P referred to as contig 7.

SEQ ID NO: 740-744 are amino acid sequences encoded by SEQ ID NO: 737.

25 SEQ ID NO: 745-750 are amino acid sequences encoded by the splice variant of P776P referred to as contig 7.

SEQ ID NO: 751 is the full-length cDNA sequence for human transmembrane protease serine 2.

30 SEQ ID NO: 752 is the amino acid sequence encoded by SEQ ID NO: 751.

SEQ ID NO: 753 is the cDNA sequence encoding the first 209 amino acids of human transmembrane protease serine 2.

SEQ ID NO: 754 is the first 209 amino acids of human transmembrane protease serine 2.

5           SEQ ID NO: 755 is the amino acid sequence of peptide 296-322 of P501S.

SEQ ID NO: 756-759 are PCR primers.

SEQ ID NO: 760 is the determined cDNA sequence of the Vb chain of a T cell receptor for the P501S-specific T cell clone 4E5.

10           SEQ ID NO: 761 is the determined cDNA sequence of the Va chain of a T cell receptor for the P501S-specific T cell clone 4E5.

SEQ ID NO: 762 is the amino acid sequence encoded by SEQ ID NO 760.

15           SEQ ID NO: 763 is the amino acid sequence encoded by SEQ ID NO 761.

SEQ ID NO: 764 is the full-length open reading frame for P768P including stop codon.

SEQ ID NO: 765 is the full-length open reading frame for P768P without stop codon.

20           SEQ ID NO: 766 is the amino acid sequence encoded by SEQ ID NO: 765.

SEQ ID NO: 767-772 are the amino acid sequences for predicted domains of P768P.

SEQ ID NO: 773 is the full-length cDNA sequence of P835P.

25           SEQ ID NO: 774 is the cDNA sequence of the previously identified clone FLJ13581.

SEQ ID NO: 775 is the cDNA sequence of the open reading frame for P835P with stop codon.

30           SEQ ID NO: 776 is the cDNA sequence of the open reading frame for P835P without stop codon.



SEQ ID NO: 777 is the full-length amino acid sequence for P835P.

SEQ ID NO: 778-785 are the amino acid sequences of extracellular and intracellular domains of P835P.

SEQ ID NO: 786 is the full-length cDNA sequence for P1000C.

5        SEQ ID NO: 787 is the cDNA sequence of the open reading frame for P1000C, including stop codon.

SEQ ID NO: 788 is the cDNA sequence of the open reading frame for P1000C, without stop codon.

SEQ ID NO: 789 is the full-length amino acid sequence for P1000C.

10        SEQ ID NO: 790 is amino acids 1-100 of SEQ ID NO: 789.

SEQ ID NO: 791 is amino acids 100-492 of SEQ ID NO: 789.

SEQ ID NO: 792 is the amino acid sequence of an  $\alpha$  prepro-P501S recombinant protein.

## 15    DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed generally to compositions and their use in the therapy and diagnosis of cancer, particularly prostate cancer. As described further below, illustrative compositions of the present invention include, but are not restricted to, polypeptides, particularly immunogenic polypeptides, polynucleotides encoding such polypeptides, antibodies and other binding agents, antigen presenting cells (APCs) and  
20    immune system cells (*e.g.*, T cells).

The practice of the present invention will employ, unless indicated specifically to the contrary, conventional methods of virology, immunology, microbiology, molecular biology and recombinant DNA techniques within the skill of  
25    the art, many of which are described below for the purpose of illustration. Such techniques are explained fully in the literature. See, *e.g.*, Sambrook, et al. *Molecular Cloning: A Laboratory Manual* (2nd Edition, 1989); Maniatis et al. *Molecular Cloning: A Laboratory Manual* (1982); DNA Cloning: A Practical Approach, vol. I & II (D. Glover, ed.); *Oligonucleotide Synthesis* (N. Gait, ed., 1984); *Nucleic Acid*

Hybridization (B. Hames & S. Higgins, eds., 1985); Transcription and Translation (B. Hames & S. Higgins, eds., 1984); Animal Cell Culture (R. Freshney, ed., 1986); Perbal, A Practical Guide to Molecular Cloning (1984).

All publications, patents and patent applications cited herein, whether  
5 supra or infra, are hereby incorporated by reference in their entirety.

As used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural references unless the content clearly dictates otherwise.

#### Polypeptide Compositions

10 As used herein, the term "polypeptide" " is used in its conventional meaning, *i.e.*, as a sequence of amino acids. The polypeptides are not limited to a specific length of the product; thus, peptides, oligopeptides, and proteins are included within the definition of polypeptide, and such terms may be used interchangeably herein unless specifically indicated otherwise. This term also does not refer to or exclude post-  
15 expression modifications of the polypeptide, for example, glycosylations, acetylations, phosphorylations and the like, as well as other modifications known in the art, both naturally occurring and non-naturally occurring. A polypeptide may be an entire protein, or a subsequence thereof. Particular polypeptides of interest in the context of this invention are amino acid subsequences comprising epitopes, *i.e.*, antigenic  
20 determinants substantially responsible for the immunogenic properties of a polypeptide and being capable of evoking an immune response.

Particularly illustrative polypeptides of the present invention comprise those encoded by a polynucleotide sequence set forth in any one of SEQ ID NOs: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382  
25 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788, or a sequence that hybridizes under moderately stringent conditions, or, alternatively, under highly stringent conditions, to a polynucleotide sequence set forth in any one of SEQ ID NOs: 1-111, 115-171, 173-175,

177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788. In specific embodiments, the polypeptides of the invention  
5 comprise amino acid sequences as set forth in any one of SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 and 789-791.

10           The polypeptides of the present invention are sometimes herein referred to as prostate-specific proteins or prostate-specific polypeptides, as an indication that their identification has been based at least in part upon their increased levels of expression in prostate tissue samples. Thus, a "prostate-specific polypeptide" or "prostate-specific protein," refers generally to a polypeptide sequence of the present  
15 invention, or a polynucleotide sequence encoding such a polypeptide, that is expressed in a substantial proportion of prostate tissue samples, for example preferably greater than about 20%, more preferably greater than about 30%, and most preferably greater than about 50% or more of prostate tissue samples tested, at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in other  
20 normal tissues, as determined using a representative assay provided herein. A prostate-specific polypeptide sequence of the invention, based upon its increased level of expression in tumor cells, has particular utility both as a diagnostic marker as well as a therapeutic target, as further described below.

          In certain preferred embodiments, the polypeptides of the invention are  
25 immunogenic, *i.e.*, they react detectably within an immunoassay (such as an ELISA or T-cell stimulation assay) with antisera and/or T-cells from a patient with prostate cancer. Screening for immunogenic activity can be performed using techniques well known to the skilled artisan. For example, such screens can be performed using methods such as those described in Harlow and Lane, *Antibodies: A Laboratory*  
30 *Manual*, Cold Spring Harbor Laboratory, 1988. In one illustrative example, a

polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, <sup>125</sup>I-labeled Protein A.

- 5                   As would be recognized by the skilled artisan, immunogenic portions of the polypeptides disclosed herein are also encompassed by the present invention. An "immunogenic portion," as used herein, is a fragment of an immunogenic polypeptide of the invention that itself is immunologically reactive (*i.e.*, specifically binds) with the B-cells and/or T-cell surface antigen receptors that recognize the polypeptide.
- 10 Immunogenic portions may generally be identified using well known techniques, such as those summarized in Paul, *Fundamental Immunology*, 3rd ed., 243-247 (Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with antigen-specific antibodies, antisera and/or T-cell lines or clones. As used herein, antisera and antibodies are "antigen-specific" if they
- 15 specifically bind to an antigen (*i.e.*, they react with the protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera and antibodies may be prepared as described herein, and using well-known techniques.

- In one preferred embodiment, an immunogenic portion of a polypeptide of the present invention is a portion that reacts with antisera and/or T-cells at a level that
- 20 is not substantially less than the reactivity of the full-length polypeptide (*e.g.*, in an ELISA and/or T-cell reactivity assay). Preferably, the level of immunogenic activity of the immunogenic portion is at least about 50%, preferably at least about 70% and most preferably greater than about 90% of the immunogenicity for the full-length polypeptide. In some instances, preferred immunogenic portions will be identified that
- 25 have a level of immunogenic activity greater than that of the corresponding full-length polypeptide, *e.g.*, having greater than about 100% or 150% or more immunogenic activity.

- In certain other embodiments, illustrative immunogenic portions may include peptides in which an N-terminal leader sequence and/or transmembrane domain
- 30 has been deleted. Other illustrative immunogenic portions will contain a small N-

and/or C-terminal deletion (*e.g.*, 1-30 amino acids, preferably 5-15 amino acids), relative to the mature protein.

In another embodiment, a polypeptide composition of the invention may also comprise one or more polypeptides that are immunologically reactive with T cells  
5 and/or antibodies generated against a polypeptide of the invention, particularly a polypeptide having an amino acid sequence disclosed herein, or to an immunogenic fragment or variant thereof.

In another embodiment of the invention, polypeptides are provided that comprise one or more polypeptides that are capable of eliciting T cells and/or antibodies  
10 that are immunologically reactive with one or more polypeptides described herein, or one or more polypeptides encoded by contiguous nucleic acid sequences contained in the polynucleotide sequences disclosed herein, or immunogenic fragments or variants thereof, or to one or more nucleic acid sequences which hybridize to one or more of these sequences under conditions of moderate to high stringency.

15 The present invention, in another aspect, provides polypeptide fragments comprising at least about 5, 10, 15, 20, 25, 50, or 100 contiguous amino acids, or more, including all intermediate lengths, of a polypeptide composition set forth herein, such as those set forth in SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568,  
20 573-586, 588-590, 592, 627-629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 and 789-791, or those encoded by a polynucleotide sequence set forth in a sequence of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591,  
25 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788.

In another aspect, the present invention provides variants of the polypeptide compositions described herein. Polypeptide variants generally encompassed by the present invention will typically exhibit at least about 70%, 75%,  
30 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% or more identity

(determined as described below), along its length, to a polypeptide sequence set forth herein.

In one preferred embodiment, the polypeptide fragments and variants provided by the present invention are immunologically reactive with an antibody and/or  
5 T-cell that reacts with a full-length polypeptide specifically set forth herein.

In another preferred embodiment, the polypeptide fragments and variants provided by the present invention exhibit a level of immunogenic activity of at least about 50%, preferably at least about 70%, and most preferably at least about 90% or more of that exhibited by a full-length polypeptide sequence specifically set forth  
10 herein.

A polypeptide "variant," as the term is used herein, is a polypeptide that typically differs from a polypeptide specifically disclosed herein in one or more substitutions, deletions, additions and/or insertions. Such variants may be naturally occurring or may be synthetically generated, for example, by modifying one or more of  
15 the above polypeptide sequences of the invention and evaluating their immunogenic activity as described herein using any of a number of techniques well known in the art.

For example, certain illustrative variants of the polypeptides of the invention include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other illustrative variants  
20 include variants in which a small portion (*e.g.*, 1-30 amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein.

In many instances, a variant will contain conservative substitutions. A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide  
25 chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. As described above, modifications may be made in the structure of the polynucleotides and polypeptides of the present invention and still obtain a functional molecule that encodes a variant or derivative polypeptide with desirable characteristics, *e.g.*, with immunogenic characteristics. When it is  
30 desired to alter the amino acid sequence of a polypeptide to create an equivalent, or

even an improved, immunogenic variant or portion of a polypeptide of the invention, one skilled in the art will typically change one or more of the codons of the encoding DNA sequence according to Table 1.

For example, certain amino acids may be substituted for other amino acids in a protein structure without appreciable loss of interactive binding capacity with structures such as, for example, antigen-binding regions of antibodies or binding sites on substrate molecules. Since it is the interactive capacity and nature of a protein that defines that protein's biological functional activity, certain amino acid sequence substitutions can be made in a protein sequence, and, of course, its underlying DNA coding sequence, and nevertheless obtain a protein with like properties. It is thus contemplated that various changes may be made in the peptide sequences of the disclosed compositions, or corresponding DNA sequences which encode said peptides without appreciable loss of their biological utility or activity.

TABLE 1

Amino Acids			Codons						
Alanine	Ala	A	GCA	GCC	GCG	GCU			
Cysteine	Cys	C	UGC	UGU					
Aspartic acid	Asp	D	GAC	GAU					
Glutamic acid	Glu	E	GAA	GAG					
Phenylalanine	Phe	F	UUC	UUU					
Glycine	Gly	G	GGA	GGC	GGG	GGU			
Histidine	His	H	CAC	CAU					
Isoleucine	Ile	I	AUA	AUC	AUU				
Lysine	Lys	K	AAA	AAG					
Leucine	Leu	L	UUA	UUG	CUA	CUC	CUG	CUU	
Methionine	Met	M	AUG						
Asparagine	Asn	N	AAC	AAU					
Proline	Pro	P	CCA	CCC	CCG	CCU			
Glutamine	Gln	Q	CAA	CAG					
Arginine	Arg	R	AGA	AGG	CGA	CGC	CGG	CGU	
Serine	Ser	S	AGC	AGU	UCA	UCC	UCG	UCU	
Threonine	Thr	T	ACA	ACC	ACG	ACU			
Valine	Val	V	GUA	GUC	GUG	GUU			
Tryptophan	Trp	W	UGG						
Tyrosine	Tyr	Y	UAC	UAU					

In making such changes, the hydropathic index of amino acids may be considered. The importance of the hydropathic amino acid index in conferring interactive biologic function on a protein is generally understood in the art (Kyte and Doolittle, 1982, incorporated herein by reference). It is accepted that the relative hydropathic character of the amino acid contributes to the secondary structure of the resultant protein, which in turn defines the interaction of the protein with other molecules, for example, enzymes, substrates, receptors, DNA, antibodies, antigens, and the like. Each amino acid has been assigned a hydropathic index on the basis of its



hydrophobicity and charge characteristics (Kyte and Doolittle, 1982). These values are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (−0.4); threonine (−0.7); serine (−0.8); tryptophan (−0.9); tyrosine (−1.3); proline (−1.6); histidine (−3.2); glutamate (−3.5);  
5 glutamine (−3.5); aspartate (−3.5); asparagine (−3.5); lysine (−3.9); and arginine (−4.5).

It is known in the art that certain amino acids may be substituted by other amino acids having a similar hydropathic index or score and still result in a protein with similar biological activity, *i.e.* still obtain a biological functionally equivalent protein. In making such changes, the substitution of amino acids whose hydropathic indices are  
10 within  $\pm 2$  is preferred, those within  $\pm 1$  are particularly preferred, and those within  $\pm 0.5$  are even more particularly preferred. It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity. U. S. Patent 4,554,101 (specifically incorporated herein by reference in its entirety), states that the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of  
15 its adjacent amino acids, correlates with a biological property of the protein.

As detailed in U. S. Patent 4,554,101, the following hydrophilicity values have been assigned to amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0  $\pm$  1); glutamate (+3.0  $\pm$  1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (−0.4); proline (−0.5  $\pm$  1); alanine (−0.5); histidine (−0.5); cysteine  
20 (−1.0); methionine (−1.3); valine (−1.5); leucine (−1.8); isoleucine (−1.8); tyrosine (−2.3); phenylalanine (−2.5); tryptophan (−3.4). It is understood that an amino acid can be substituted for another having a similar hydrophilicity value and still obtain a biologically equivalent, and in particular, an immunologically equivalent protein. In such changes, the substitution of amino acids whose hydrophilicity values are within  $\pm 2$   
25 is preferred, those within  $\pm 1$  are particularly preferred, and those within  $\pm 0.5$  are even more particularly preferred.

As outlined above, amino acid substitutions are generally therefore based on the relative similarity of the amino acid side-chain substituents, for example, their hydrophobicity, hydrophilicity, charge, size, and the like. Exemplary substitutions that  
30 take various of the foregoing characteristics into consideration are well known to those

of skill in the art and include: arginine and lysine; glutamate and aspartate; serine and threonine; glutamine and asparagine; and valine, leucine and isoleucine.

In addition, any polynucleotide may be further modified to increase stability *in vivo*. Possible modifications include, but are not limited to, the addition of  
5 flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such as inosine, queosine and wybutosine, as well as acetyl-methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

10 Amino acid substitutions may further be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values  
15 include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain nonconservative changes. In a  
20 preferred embodiment, variant polypeptides differ from a native sequence by substitution, deletion or addition of five amino acids or fewer. Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydrophobic nature of the polypeptide.

25 As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein, which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (e.g., poly-His), or to enhance binding of the polypeptide to a solid support. For  
30 example, a polypeptide may be conjugated to an immunoglobulin Fc region.

When comparing polypeptide sequences, two sequences are said to be "identical" if the sequence of amino acids in the two sequences is the same when aligned for maximum correspondence, as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison  
5 window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

10 Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships.  
15 In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenies pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS* 5:151-153; Myers, E.W. and Muller W. (1988) *CABIOS* 4:11-17; Robinson,  
20 E.D. (1971) *Comb. Theor* 11:105; Santou, N. Nes, M. (1987) *Mol. Biol. Evol.* 4:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad. Sci. USA* 80:726-730.

Alternatively, optimal alignment of sequences for comparison may be  
25 conducted by the local identity algorithm of Smith and Waterman (1981) *Add. APL Math* 2:482, by the identity alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity methods of Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85: 2444, by computerized implementations of these algorithms (GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics

Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by inspection.

One preferred example of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al. (1977) *Nucl. Acids Res.* 25:3389-3402 and Altschul et al. (1990) *J. Mol. Biol.* 215:403-410, respectively. BLAST and BLAST 2.0 can be used, for example with the parameters described herein, to determine percent sequence identity for the polynucleotides and polypeptides of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. For amino acid sequences, a scoring matrix can be used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment.

In one preferred approach, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polypeptide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.*, the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Within other illustrative embodiments, a polypeptide may be a fusion polypeptide that comprises multiple polypeptides as described herein, or that comprises at least one polypeptide as described herein and an unrelated sequence, such as a known

tumor protein. A fusion partner may, for example, assist in providing T helper epitopes (an immunological fusion partner), preferably T helper epitopes recognized by humans, or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological  
5 and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the polypeptide or to enable the polypeptide to be targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the polypeptide.

Fusion polypeptides may generally be prepared using standard  
10 techniques, including chemical conjugation. Preferably, a fusion polypeptide is expressed as a recombinant polypeptide, allowing the production of increased levels, relative to a non-fused polypeptide, in an expression system. Briefly, DNA sequences encoding the polypeptide components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one  
15 polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase. This permits translation into a single fusion polypeptide that retains the biological activity of both component polypeptides.

A peptide linker sequence may be employed to separate the first and  
20 second polypeptide components by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion polypeptide using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a  
25 secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as  
30 linkers include those disclosed in Maratea et al., *Gene* 40:39-46, 1985; Murphy et al.,

*Proc. Natl. Acad. Sci. USA* 83:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to  
5 separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and  
10 transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

The fusion polypeptide can comprise a polypeptide as described herein together with an unrelated immunogenic protein, such as an immunogenic protein capable of eliciting a recall response. Examples of such proteins include tetanus,  
15 tuberculosis and hepatitis proteins (*see, for example, Stoute et al. New Engl. J. Med.*, 336:86-91, 1997).

In one preferred embodiment, the immunological fusion partner is derived from a *Mycobacterium* sp., such as a *Mycobacterium tuberculosis*-derived Ra12 fragment. Ra12 compositions and methods for their use in enhancing the expression  
20 and/or immunogenicity of heterologous polynucleotide/polypeptide sequences is described in U.S. Patent Application 60/158,585, the disclosure of which is incorporated herein by reference in its entirety. Briefly, Ra12 refers to a polynucleotide region that is a subsequence of a *Mycobacterium tuberculosis* MTB32A nucleic acid. MTB32A is a serine protease of 32 KD molecular weight encoded by a gene in virulent  
25 and avirulent strains of *M. tuberculosis*. The nucleotide sequence and amino acid sequence of MTB32A have been described (for example, U.S. Patent Application 60/158,585; *see also, Skeiky et al., Infection and Immun.* (1999) 67:3998-4007, incorporated herein by reference). C-terminal fragments of the MTB32A coding sequence express at high levels and remain as a soluble polypeptides throughout the  
30 purification process. Moreover, Ra12 may enhance the immunogenicity of heterologous

immunogenic polypeptides with which it is fused. One preferred Ra12 fusion polypeptide comprises a 14 KD C-terminal fragment corresponding to amino acid residues 192 to 323 of MTB32A. Other preferred Ra12 polynucleotides generally comprise at least about 15 consecutive nucleotides, at least about 30 nucleotides, at least about 60 nucleotides, at least about 100 nucleotides, at least about 200 nucleotides, or at least about 300 nucleotides that encode a portion of a Ra12 polypeptide. Ra12 polynucleotides may comprise a native sequence (*i.e.*, an endogenous sequence that encodes a Ra12 polypeptide or a portion thereof) or may comprise a variant of such a sequence. Ra12 polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions such that the biological activity of the encoded fusion polypeptide is not substantially diminished, relative to a fusion polypeptide comprising a native Ra12 polypeptide. Variants preferably exhibit at least about 70% identity, more preferably at least about 80% identity and most preferably at least about 90% identity to a polynucleotide sequence that encodes a native Ra12 polypeptide or a portion thereof.

Within other preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium *Haemophilus influenza B* (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third of the protein (*e.g.*, the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in *E. coli* (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen presenting cells. Other fusion partners include the non-structural protein from influenzae virus, NS1 (hemagglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is derived from *Streptococcus pneumoniae*, which synthesizes an N-acetyl-L-alanine

amidase known as amidase LYTA (encoded by the *LytA* gene; *Gene* 43:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This property has been exploited for the development of *E. coli* C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at the amino terminus has been described (see *Biotechnology* 10:795-798, 1992). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion polypeptide. A repeat portion is found in the C-terminal region starting at residue 178. A particularly preferred repeat portion incorporates residues 188-305.

Yet another illustrative embodiment involves fusion polypeptides, and the polynucleotides encoding them, wherein the fusion partner comprises a targeting signal capable of directing a polypeptide to the endosomal/lysosomal compartment, as described in U.S. Patent No. 5,633,234. An immunogenic polypeptide of the invention, when fused with this targeting signal, will associate more efficiently with MHC class II molecules and thereby provide enhanced in vivo stimulation of CD4<sup>+</sup> T-cells specific for the polypeptide.

Polypeptides of the invention are prepared using any of a variety of well known synthetic and/or recombinant techniques, the latter of which are further described below. Polypeptides, portions and other variants generally less than about 150 amino acids can be generated by synthetic means, using techniques well known to those of ordinary skill in the art. In one illustrative example, such polypeptides are synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. See Merrifield, *J. Am. Chem. Soc.* 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

In general, polypeptide compositions (including fusion polypeptides) of the invention are isolated. An "isolated" polypeptide is one that is removed from its



original environment. For example, a naturally-occurring protein or polypeptide is isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are also purified, *e.g.*, are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99%  
5 pure.

#### Polynucleotide Compositions

The present invention, in other aspects, provides polynucleotide compositions. The terms "DNA" and "polynucleotide" are used essentially interchangeably herein to refer to a DNA molecule that has been isolated free of total  
10 genomic DNA of a particular species. "Isolated," as used herein, means that a polynucleotide is substantially away from other coding sequences, and that the DNA molecule does not contain large portions of unrelated coding DNA, such as large chromosomal fragments or other functional genes or polypeptide coding regions. Of course, this refers to the DNA molecule as originally isolated, and does not exclude  
15 genes or coding regions later added to the segment by the hand of man.

As will be understood by those skilled in the art, the polynucleotide compositions of this invention can include genomic sequences, extra-genomic and plasmid-encoded sequences and smaller engineered gene segments that express, or may be adapted to express, proteins, polypeptides, peptides and the like. Such segments may  
20 be naturally isolated, or modified synthetically by the hand of man.

As will be also recognized by the skilled artisan, polynucleotides of the invention may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules may include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-  
25 to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

Polynucleotides may comprise a native sequence (*i.e.*, an endogenous sequence that encodes a polypeptide/protein of the invention or a portion thereof) or may comprise a sequence that encodes a variant or derivative, preferably an immunogenic variant or derivative, of such a sequence.

5           Therefore, according to another aspect of the present invention, polynucleotide compositions are provided that comprise some or all of a polynucleotide sequence set forth in any one of SEQ ID NOs: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 10 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788, complements of a polynucleotide sequence set forth in any one of SEQ ID NOs: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 15 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788, and degenerate variants of a polynucleotide sequence set forth in any one of SEQ ID NOs: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 20 773-776 and 786-788. In certain preferred embodiments, the polynucleotide sequences set forth herein encode immunogenic polypeptides, as described above.

          In other related embodiments, the present invention provides polynucleotide variants having substantial identity to the sequences disclosed herein in SEQ ID NOs: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332- 25 335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788, for example those comprising at least 70% sequence identity, preferably at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% or higher, sequence identity compared to a 30 polynucleotide sequence of this invention using the methods described herein, (*e.g.*,

BLAST analysis using standard parameters, as described below). One skilled in this art will recognize that these values can be appropriately adjusted to determine corresponding identity of proteins encoded by two nucleotide sequences by taking into account codon degeneracy, amino acid similarity, reading frame positioning and the  
5 like.

Typically, polynucleotide variants will contain one or more substitutions, additions, deletions and/or insertions, preferably such that the immunogenicity of the polypeptide encoded by the variant polynucleotide is not substantially diminished relative to a polypeptide encoded by a polynucleotide sequence specifically set forth  
10 herein). The term "variants" should also be understood to encompass homologous genes of xenogenic origin.

In additional embodiments, the present invention provides polynucleotide fragments comprising various lengths of contiguous stretches of sequence identical to, or complementary to, one or more of the sequences disclosed  
15 herein. For example, polynucleotides are provided by this invention that comprise at least about 10, 15, 20, 30, 40, 50, 75, 100, 150, 200, 300, 400, 500 or 1000 or more contiguous nucleotides of one or more of the sequences disclosed herein as well as all intermediate lengths there between. It will be readily understood that "intermediate lengths", in this context, means any length between the quoted values, such as 16, 17,  
20 18, 19, *etc.*; 21, 22, 23, *etc.*; 30, 31, 32, *etc.*; 50, 51, 52, 53, *etc.*; 100, 101, 102, 103, *etc.*; 150, 151, 152, 153, *etc.*; including all integers through 200-500; 500-1,000, and the like.

In another embodiment of the invention, polynucleotide compositions are provided that are capable of hybridizing under moderate to high stringency conditions to  
25 a polynucleotide sequence provided herein, or a fragment thereof, or a complementary sequence thereof. Hybridization techniques are well known in the art of molecular biology. For purposes of illustration, suitable moderately stringent conditions for testing the hybridization of a polynucleotide of this invention with other polynucleotides include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0);  
30 hybridizing at 50°C-60°C, 5 X SSC, overnight; followed by washing twice at 65°C for

20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS. One skilled in the art will understand that the stringency of hybridization can be readily manipulated, such as by altering the salt content of the hybridization solution and/or the temperature at which the hybridization is performed. For example, in another embodiment, suitable  
5 highly stringent hybridization conditions include those described above, with the exception that the temperature of hybridization is increased, *e.g.*, to 60-65°C or 65-70°C.

In certain preferred embodiments, the polynucleotides described above, *e.g.*, polynucleotide variants, fragments and hybridizing sequences, encode polypeptides  
10 that are immunologically cross-reactive with a polypeptide sequence specifically set forth herein. In other preferred embodiments, such polynucleotides encode polypeptides that have a level of immunogenic activity of at least about 50%, preferably at least about 70%, and more preferably at least about 90% of that for a polypeptide sequence specifically set forth herein.

15 The polynucleotides of the present invention, or fragments thereof, regardless of the length of the coding sequence itself, may be combined with other DNA sequences, such as promoters, polyadenylation signals, additional restriction enzyme sites, multiple cloning sites, other coding segments, and the like, such that their overall length may vary considerably. It is therefore contemplated that a nucleic acid fragment  
20 of almost any length may be employed, with the total length preferably being limited by the ease of preparation and use in the intended recombinant DNA protocol. For example, illustrative polynucleotide segments with total lengths of about 10,000, about 5000, about 3000, about 2,000, about 1,000, about 500, about 200, about 100, about 50 base pairs in length, and the like, (including all intermediate lengths) are contemplated  
25 to be useful in many implementations of this invention.

When comparing polynucleotide sequences, two sequences are said to be "identical" if the sequence of nucleotides in the two sequences is the same when aligned for maximum correspondence, as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison  
30 window to identify and compare local regions of sequence similarity. A "comparison

window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, preferably 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

- 5                   Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships.
- 10 In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenies pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS* 5:151-153; Myers, E.W. and Muller W. (1988) *CABIOS* 4:11-17; Robinson,
- 15 E.D. (1971) *Comb. Theor* 11:105; Santou, N. Nes, M. (1987) *Mol. Biol. Evol.* 4:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad. Sci. USA* 80:726-730.

- Alternatively, optimal alignment of sequences for comparison may be
- 20 conducted by the local identity algorithm of Smith and Waterman (1981) *Add. APL. Math* 2:482, by the identity alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity methods of Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85: 2444, by computerized implementations of these algorithms (GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics
- 25 Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by inspection.

- One preferred example of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al. (1977) *Nucl. Acids Res.* 25:3389-3402
- 30 and Altschul et al. (1990) *J. Mol. Biol.* 215:403-410, respectively. BLAST and BLAST

2.0 can be used, for example with the parameters described herein, to determine percent sequence identity for the polynucleotides of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. In one illustrative example, cumulative scores can be calculated using, for  
5 nucleotide sequences, the parameters M (reward score for a pair of matching residues; always >0) and N (penalty score for mismatching residues; always <0). Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments;  
10 or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, and expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff and Henikoff (1989) *Proc. Natl. Acad. Sci. USA* 89:10915) alignments, (B) of 50, expectation (E) of 10, M=5, N=-4 and  
15 a comparison of both strands.

Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) of 20 percent or less, usually 5  
20 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the  
25 reference sequence (*i.e.*, the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal  
30 homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides

that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions  
5 and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

Therefore, in another embodiment of the invention, a mutagenesis approach, such as site-specific mutagenesis, is employed for the preparation of  
10 immunogenic variants and/or derivatives of the polypeptides described herein. By this approach, specific modifications in a polypeptide sequence can be made through mutagenesis of the underlying polynucleotides that encode them. These techniques provides a straightforward approach to prepare and test sequence variants, for example, incorporating one or more of the foregoing considerations, by introducing one or more  
15 nucleotide sequence changes into the polynucleotide.

Site-specific mutagenesis allows the production of mutants through the use of specific oligonucleotide sequences which encode the DNA sequence of the desired mutation, as well as a sufficient number of adjacent nucleotides, to provide a primer sequence of sufficient size and sequence complexity to form a stable duplex on  
20 both sides of the deletion junction being traversed. Mutations may be employed in a selected polynucleotide sequence to improve, alter, decrease, modify, or otherwise change the properties of the polynucleotide itself, and/or alter the properties, activity, composition, stability, or primary sequence of the encoded polypeptide.

In certain embodiments of the present invention, the inventors  
25 contemplate the mutagenesis of the disclosed polynucleotide sequences to alter one or more properties of the encoded polypeptide, such as the immunogenicity of a polypeptide vaccine. The techniques of site-specific mutagenesis are well-known in the art, and are widely used to create variants of both polypeptides and polynucleotides. For example, site-specific mutagenesis is often used to alter a specific portion of a DNA  
30 molecule. In such embodiments, a primer comprising typically about 14 to about 25

nucleotides or so in length is employed, with about 5 to about 10 residues on both sides of the junction of the sequence being altered.

As will be appreciated by those of skill in the art, site-specific mutagenesis techniques have often employed a phage vector that exists in both a single stranded and double stranded form. Typical vectors useful in site-directed mutagenesis include vectors such as the M13 phage. These phage are readily commercially-available and their use is generally well-known to those skilled in the art. Double-stranded plasmids are also routinely employed in site directed mutagenesis that eliminates the step of transferring the gene of interest from a plasmid to a phage.

10 In general, site-directed mutagenesis in accordance herewith is performed by first obtaining a single-stranded vector or melting apart of two strands of a double-stranded vector that includes within its sequence a DNA sequence that encodes the desired peptide. An oligonucleotide primer bearing the desired mutated sequence is prepared, generally synthetically. This primer is then annealed with the single-stranded  
15 vector, and subjected to DNA polymerizing enzymes such as *E. coli* polymerase I Klenow fragment, in order to complete the synthesis of the mutation-bearing strand. Thus, a heteroduplex is formed wherein one strand encodes the original non-mutated sequence and the second strand bears the desired mutation. This heteroduplex vector is then used to transform appropriate cells, such as *E. coli* cells, and clones are selected  
20 which include recombinant vectors bearing the mutated sequence arrangement.

The preparation of sequence variants of the selected peptide-encoding DNA segments using site-directed mutagenesis provides a means of producing potentially useful species and is not meant to be limiting as there are other ways in which sequence variants of peptides and the DNA sequences encoding them may be  
25 obtained. For example, recombinant vectors encoding the desired peptide sequence may be treated with mutagenic agents, such as hydroxylamine, to obtain sequence variants. Specific details regarding these methods and protocols are found in the teachings of Maloy *et al.*, 1994; Segal, 1976; Prokop and Bajpai, 1991; Kuby, 1994; and Maniatis *et al.*, 1982, each incorporated herein by reference, for that purpose.



As used herein, the term "oligonucleotide directed mutagenesis procedure" refers to template-dependent processes and vector-mediated propagation which result in an increase in the concentration of a specific nucleic acid molecule relative to its initial concentration, or in an increase in the concentration of a detectable  
5 signal, such as amplification. As used herein, the term "oligonucleotide directed mutagenesis procedure" is intended to refer to a process that involves the template-dependent extension of a primer molecule. The term template dependent process refers to nucleic acid synthesis of an RNA or a DNA molecule wherein the sequence of the newly synthesized strand of nucleic acid is dictated by the well-known  
10 rules of complementary base pairing (see, for example, Watson, 1987). Typically, vector mediated methodologies involve the introduction of the nucleic acid fragment into a DNA or RNA vector, the clonal amplification of the vector, and the recovery of the amplified nucleic acid fragment. Examples of such methodologies are provided by U. S. Patent No. 4,237,224, specifically incorporated herein by reference in its entirety.

15 In another approach for the production of polypeptide variants of the present invention, recursive sequence recombination, as described in U.S. Patent No. 5,837,458, may be employed. In this approach, iterative cycles of recombination and screening or selection are performed to "evolve" individual polynucleotide variants of the invention having, for example, enhanced immunogenic activity.

20 In other embodiments of the present invention, the polynucleotide sequences provided herein can be advantageously used as probes or primers for nucleic acid hybridization. As such, it is contemplated that nucleic acid segments that comprise a sequence region of at least about 15 contiguous nucleotides that has the same sequence as, or is complementary to, a 15 nucleotide long contiguous sequence  
25 disclosed herein will find particular utility. Longer contiguous identical or complementary sequences, *e.g.*, those of about 20, 30, 40, 50, 100, 200, 500, 1000 (including all intermediate lengths) and even up to full length sequences will also be of use in certain embodiments.

The ability of such nucleic acid probes to specifically hybridize to a  
30 sequence of interest will enable them to be of use in detecting the presence of

complementary sequences in a given sample. However, other uses are also envisioned, such as the use of the sequence information for the preparation of mutant species primers, or primers for use in preparing other genetic constructions.

Polynucleotide molecules having sequence regions consisting of  
5 contiguous nucleotide stretches of 10-14, 15-20, 30, 50, or even of 100-200 nucleotides or so (including intermediate lengths as well), identical or complementary to a polynucleotide sequence disclosed herein, are particularly contemplated as hybridization probes for use in, *e.g.*, Southern and Northern blotting. This would allow a gene product, or fragment thereof, to be analyzed, both in diverse cell types and also in  
10 various bacterial cells. The total size of fragment, as well as the size of the complementary stretch(es), will ultimately depend on the intended use or application of the particular nucleic acid segment. Smaller fragments will generally find use in hybridization embodiments, wherein the length of the contiguous complementary region may be varied, such as between about 15 and about 100 nucleotides, but larger  
15 contiguous complementarity stretches may be used, according to the length complementary sequences one wishes to detect.

The use of a hybridization probe of about 15-25 nucleotides in length allows the formation of a duplex molecule that is both stable and selective. Molecules having contiguous complementary sequences over stretches greater than 15 bases in  
20 length are generally preferred, though, in order to increase stability and selectivity of the hybrid, and thereby improve the quality and degree of specific hybrid molecules obtained. One will generally prefer to design nucleic acid molecules having gene-complementary stretches of 15 to 25 contiguous nucleotides, or even longer where desired.

25 Hybridization probes may be selected from any portion of any of the sequences disclosed herein. All that is required is to review the sequences set forth herein, or to any continuous portion of the sequences, from about 15-25 nucleotides in length up to and including the full length sequence, that one wishes to utilize as a probe or primer. The choice of probe and primer sequences may be governed by various

factors. For example, one may wish to employ primers from towards the termini of the total sequence.

Small polynucleotide segments or fragments may be readily prepared by, for example, directly synthesizing the fragment by chemical means, as is commonly practiced using an automated oligonucleotide synthesizer. Also, fragments may be obtained by application of nucleic acid reproduction technology, such as the PCR™ technology of U. S. Patent 4,683,202 (incorporated herein by reference), by introducing selected sequences into recombinant vectors for recombinant production, and by other recombinant DNA techniques generally known to those of skill in the art of molecular biology.

The nucleotide sequences of the invention may be used for their ability to selectively form duplex molecules with complementary stretches of the entire gene or gene fragments of interest. Depending on the application envisioned, one will typically desire to employ varying conditions of hybridization to achieve varying degrees of selectivity of probe towards target sequence. For applications requiring high selectivity, one will typically desire to employ relatively stringent conditions to form the hybrids, *e.g.*, one will select relatively low salt and/or high temperature conditions, such as provided by a salt concentration of from about 0.02 M to about 0.15 M salt at temperatures of from about 50°C to about 70°C. Such selective conditions tolerate little, if any, mismatch between the probe and the template or target strand, and would be particularly suitable for isolating related sequences.

Of course, for some applications, for example, where one desires to prepare mutants employing a mutant primer strand hybridized to an underlying template, less stringent (reduced stringency) hybridization conditions will typically be needed in order to allow formation of the heteroduplex. In these circumstances, one may desire to employ salt conditions such as those of from about 0.15 M to about 0.9 M salt, at temperatures ranging from about 20°C to about 55°C. Cross-hybridizing species can thereby be readily identified as positively hybridizing signals with respect to control hybridizations. In any case, it is generally appreciated that conditions can be rendered more stringent by the addition of increasing amounts of formamide, which serves to

destabilize the hybrid duplex in the same manner as increased temperature. Thus, hybridization conditions can be readily manipulated, and thus will generally be a method of choice depending on the desired results.

According to another embodiment of the present invention,  
5 polynucleotide compositions comprising antisense oligonucleotides are provided. Antisense oligonucleotides have been demonstrated to be effective and targeted inhibitors of protein synthesis, and, consequently, provide a therapeutic approach by which a disease can be treated by inhibiting the synthesis of proteins that contribute to the disease. The efficacy of antisense oligonucleotides for inhibiting protein synthesis  
10 is well established. For example, the synthesis of polygalacturonase and the muscarine type 2 acetylcholine receptor are inhibited by antisense oligonucleotides directed to their respective mRNA sequences (U. S. Patent 5,739,119 and U. S. Patent 5,759,829). Further, examples of antisense inhibition have been demonstrated with the nuclear protein cyclin, the multiple drug resistance gene (MDG1), ICAM-1, E-selectin, STK-1,  
15 striatal GABA<sub>A</sub> receptor and human EGF (Jaskulski *et al.*, Science. 1988 Jun 10;240(4858):1544-6; Vasanthakumar and Ahmed, Cancer Commun. 1989;1(4):225-32; Peris *et al.*, Brain Res Mol Brain Res. 1998 Jun 15;57(2):310-20; U. S. Patent 5,801,154; U.S. Patent 5,789,573; U. S. Patent 5,718,709 and U.S. Patent 5,610,288). Antisense constructs have also been described that inhibit and can be used to treat a  
20 variety of abnormal cellular proliferations, *e.g.* cancer (U. S. Patent 5,747,470; U. S. Patent 5,591,317 and U. S. Patent 5,783,683).

Therefore, in certain embodiments, the present invention provides oligonucleotide sequences that comprise all, or a portion of, any sequence that is capable of specifically binding to polynucleotide sequence described herein, or a  
25 complement thereof. In one embodiment, the antisense oligonucleotides comprise DNA or derivatives thereof. In another embodiment, the oligonucleotides comprise RNA or derivatives thereof. In a third embodiment, the oligonucleotides are modified DNAs comprising a phosphorothioated modified backbone. In a fourth embodiment, the oligonucleotide sequences comprise peptide nucleic acids or derivatives thereof. In  
30 each case, preferred compositions comprise a sequence region that is complementary,

and more preferably substantially-complementary, and even more preferably, completely complementary to one or more portions of polynucleotides disclosed herein. Selection of antisense compositions specific for a given gene sequence is based upon analysis of the chosen target sequence and determination of secondary structure,  $T_m$ ,  
5 binding energy, and relative stability. Antisense compositions may be selected based upon their relative inability to form dimers, hairpins, or other secondary structures that would reduce or prohibit specific binding to the target mRNA in a host cell. Highly preferred target regions of the mRNA, are those which are at or near the AUG translation initiation codon, and those sequences which are substantially complementary  
10 to 5' regions of the mRNA. These secondary structure analyses and target site selection considerations can be performed, for example, using v.4 of the OLIGO primer analysis software and/or the BLASTN 2.0.5 algorithm software (Altschul *et al.*, Nucleic Acids Res. 1997 Sep 1;25(17):3389-402).

The use of an antisense delivery method employing a short peptide  
15 vector, termed MPG (27 residues), is also contemplated. The MPG peptide contains a hydrophobic domain derived from the fusion sequence of HIV gp41 and a hydrophilic domain from the nuclear localization sequence of SV40 T-antigen (Morris *et al.*, Nucleic Acids Res. 1997 Jul 15;25(14):2730-6). It has been demonstrated that several molecules of the MPG peptide coat the antisense oligonucleotides and can be delivered  
20 into cultured mammalian cells in less than 1 hour with relatively high efficiency (90%). Further, the interaction with MPG strongly increases both the stability of the oligonucleotide to nuclease and the ability to cross the plasma membrane.

According to another embodiment of the invention, the polynucleotide compositions described herein are used in the design and preparation of ribozyme  
25 molecules for inhibiting expression of the tumor polypeptides and proteins of the present invention in tumor cells. Ribozymes are RNA-protein complexes that cleave nucleic acids in a site-specific fashion. Ribozymes have specific catalytic domains that possess endonuclease activity (Kim and Cech, Proc Natl Acad Sci U S A. 1987 Dec;84(24):8788-92; Forster and Symons, Cell. 1987 Apr 24;49(2):211-20). For  
30 example, a large number of ribozymes accelerate phosphoester transfer reactions with a

high degree of specificity, often cleaving only one of several phosphoesters in an oligonucleotide substrate (Cech *et al.*, Cell. 1981 Dec;27(3 Pt 2):487-96; Michel and Westhof, J Mol Biol. 1990 Dec 5;216(3):585-610; Reinhold-Hurek and Shub, Nature. 1992 May 14;357(6374):173-6). This specificity has been attributed to the requirement  
5 that the substrate bind via specific base-pairing interactions to the internal guide sequence ("IGS") of the ribozyme prior to chemical reaction.

Six basic varieties of naturally-occurring enzymatic RNAs are known presently. Each can catalyze the hydrolysis of RNA phosphodiester bonds *in trans* (and thus can cleave other RNA molecules) under physiological conditions. In general,  
10 enzymatic nucleic acids act by first binding to a target RNA. Such binding occurs through the target binding portion of a enzymatic nucleic acid which is held in close proximity to an enzymatic portion of the molecule that acts to cleave the target RNA. Thus, the enzymatic nucleic acid first recognizes and then binds a target RNA through complementary base-pairing, and once bound to the correct site, acts enzymatically to  
15 cut the target RNA. Strategic cleavage of such a target RNA will destroy its ability to direct synthesis of an encoded protein. After an enzymatic nucleic acid has bound and cleaved its RNA target, it is released from that RNA to search for another target and can repeatedly bind and cleave new targets.

The enzymatic nature of a ribozyme is advantageous over many  
20 technologies, such as antisense technology (where a nucleic acid molecule simply binds to a nucleic acid target to block its translation) since the concentration of ribozyme necessary to affect a therapeutic treatment is lower than that of an antisense oligonucleotide. This advantage reflects the ability of the ribozyme to act enzymatically. Thus, a single ribozyme molecule is able to cleave many molecules of  
25 target RNA. In addition, the ribozyme is a highly specific inhibitor, with the specificity of inhibition depending not only on the base pairing mechanism of binding to the target RNA, but also on the mechanism of target RNA cleavage. Single mismatches, or base-substitutions, near the site of cleavage can completely eliminate catalytic activity of a ribozyme. Similar mismatches in antisense molecules do not prevent their action  
30 (Woolf *et al.*, Proc Natl Acad Sci U S A. 1992 Aug 15;89(16):7305-9). Thus, the

specificity of action of a ribozyme is greater than that of an antisense oligonucleotide binding the same RNA site.

The enzymatic nucleic acid molecule may be formed in a hammerhead, hairpin, a hepatitis  $\delta$  virus, group I intron or RNaseP RNA (in association with an RNA  
5 guide sequence) or Neurospora VS RNA motif. Examples of hammerhead motifs are described by Rossi *et al.* Nucleic Acids Res. 1992 Sep 11;20(17):4559-65. Examples of hairpin motifs are described by Hampel *et al.* (Eur. Pat. Appl. Publ. No. EP 0360257), Hampel and Tritz, Biochemistry 1989 Jun 13;28(12):4929-33; Hampel *et al.*, Nucleic  
10 Acids Res. 1990 Jan 25;18(2):299-304 and U. S. Patent 5,631,359. An example of the hepatitis  $\delta$  virus motif is described by Perrotta and Been, Biochemistry. 1992 Dec 1;31(47):11843-52; an example of the RNaseP motif is described by Guerrier-Takada  
*et al.*, Cell. 1983 Dec;35(3 Pt 2):849-57; Neurospora VS RNA ribozyme motif is described by Collins (Saville and Collins, Cell. 1990 May 18;61(4):685-96; Saville and Collins, Proc Natl Acad Sci U S A. 1991 Oct 1;88(19):8826-30; Collins and Olive,  
15 Biochemistry. 1993 Mar 23;32(11):2795-9); and an example of the Group I intron is described in (U. S. Patent 4,987,071). All that is important in an enzymatic nucleic acid molecule of this invention is that it has a specific substrate binding site which is complementary to one or more of the target gene RNA regions, and that it have  
20 nucleotide sequences within or surrounding that substrate binding site which impart an RNA cleaving activity to the molecule. Thus the ribozyme constructs need not be limited to specific motifs mentioned herein.

Ribozymes may be designed as described in Int. Pat. Appl. Publ. No. WO 93/23569 and Int. Pat. Appl. Publ. No. WO 94/02595, each specifically incorporated herein by reference) and synthesized to be tested *in vitro* and *in vivo*, as  
25 described. Such ribozymes can also be optimized for delivery. While specific examples are provided, those in the art will recognize that equivalent RNA targets in other species can be utilized when necessary.

Ribozyme activity can be optimized by altering the length of the ribozyme binding arms, or chemically synthesizing ribozymes with modifications that  
30 prevent their degradation by serum ribonucleases (see *e.g.*, Int. Pat. Appl. Publ. No. WO

92/07065; Int. Pat. Appl. Publ. No. WO 93/15187; Int. Pat. Appl. Publ. No. WO 91/03162; Eur. Pat. Appl. Publ. No. 92110298.4; U. S. Patent 5,334,711; and Int. Pat. Appl. Publ. No. WO 94/13688, which describe various chemical modifications that can be made to the sugar moieties of enzymatic RNA molecules), modifications which enhance their efficacy in cells, and removal of stem II bases to shorten RNA synthesis times and reduce chemical requirements.

Sullivan *et al.* (Int. Pat. Appl. Publ. No. WO 94/02595) describes the general methods for delivery of enzymatic RNA molecules. Ribozymes may be administered to cells by a variety of methods known to those familiar to the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as hydrogels, cyclodextrins, biodegradable nanocapsules, and bioadhesive microspheres. For some indications, ribozymes may be directly delivered *ex vivo* to cells or tissues with or without the aforementioned vehicles. Alternatively, the RNA/vehicle combination may be locally delivered by direct inhalation, by direct injection or by use of a catheter, infusion pump or stent. Other routes of delivery include, but are not limited to, intravascular, intramuscular, subcutaneous or joint injection, aerosol inhalation, oral (tablet or pill form), topical, systemic, ocular, intraperitoneal and/or intrathecal delivery. More detailed descriptions of ribozyme delivery and administration are provided in Int. Pat. Appl. Publ. No. WO 94/02595 and Int. Pat. Appl. Publ. No. WO 93/23569, each specifically incorporated herein by reference.

Another means of accumulating high concentrations of a ribozyme(s) within cells is to incorporate the ribozyme-encoding sequences into a DNA expression vector. Transcription of the ribozyme sequences are driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA polymerase III (pol III). Transcripts from pol II or pol III promoters will be expressed at high levels in all cells; the levels of a given pol II promoter in a given cell type will depend on the nature of the gene regulatory sequences (enhancers, silencers, *etc.*) present nearby. Prokaryotic RNA polymerase promoters may also be used, providing that the prokaryotic RNA polymerase enzyme is expressed in the appropriate cells. Ribozymes



expressed from such promoters have been shown to function in mammalian cells. Such transcription units can be incorporated into a variety of vectors for introduction into mammalian cells, including but not restricted to, plasmid DNA vectors, viral DNA vectors (such as adenovirus or adeno-associated vectors), or viral RNA vectors (such as retroviral, semliki forest virus, sindbis virus vectors).

In another embodiment of the invention, peptide nucleic acids (PNAs) compositions are provided. PNA is a DNA mimic in which the nucleobases are attached to a pseudopeptide backbone (Good and Nielsen, *Antisense Nucleic Acid Drug Dev.* 1997 7(4) 431-37). PNA is able to be utilized in a number methods that traditionally have used RNA or DNA. Often PNA sequences perform better in techniques than the corresponding RNA or DNA sequences and have utilities that are not inherent to RNA or DNA. A review of PNA including methods of making, characteristics of, and methods of using, is provided by Corey (*Trends Biotechnol* 1997 Jun;15(6):224-9). As such, in certain embodiments, one may prepare PNA sequences that are complementary to one or more portions of the ACE mRNA sequence, and such PNA compositions may be used to regulate, alter, decrease, or reduce the translation of ACE-specific mRNA, and thereby alter the level of ACE activity in a host cell to which such PNA compositions have been administered.

PNAs have 2-aminoethyl-glycine linkages replacing the normal phosphodiester backbone of DNA (Nielsen *et al.*, *Science* 1991 Dec 6;254(5037):1497-500; Hanvey *et al.*, *Science*. 1992 Nov 27;258(5087):1481-5; Hyrup and Nielsen, *Bioorg Med Chem.* 1996 Jan;4(1):5-23). This chemistry has three important consequences: firstly, in contrast to DNA or phosphorothioate oligonucleotides, PNAs are neutral molecules; secondly, PNAs are achiral, which avoids the need to develop a stereoselective synthesis; and thirdly, PNA synthesis uses standard Boc or Fmoc protocols for solid-phase peptide synthesis, although other methods, including a modified Merrifield method, have been used.

PNA monomers or ready-made oligomers are commercially available from PerSeptive Biosystems (Framingham, MA). PNA syntheses by either Boc or Fmoc protocols are straightforward using manual or automated protocols (Norton *et al.*,

Bioorg Med Chem. 1995 Apr;3(4):437-45). The manual protocol lends itself to the production of chemically modified PNAs or the simultaneous synthesis of families of closely related PNAs.

As with peptide synthesis, the success of a particular PNA synthesis will  
5 depend on the properties of the chosen sequence. For example, while in theory PNAs can incorporate any combination of nucleotide bases, the presence of adjacent purines can lead to deletions of one or more residues in the product. In expectation of this difficulty, it is suggested that, in producing PNAs with adjacent purines, one should repeat the coupling of residues likely to be added inefficiently. This should be followed  
10 by the purification of PNAs by reverse-phase high-pressure liquid chromatography, providing yields and purity of product similar to those observed during the synthesis of peptides.

Modifications of PNAs for a given application may be accomplished by coupling amino acids during solid-phase synthesis or by attaching compounds that  
15 contain a carboxylic acid group to the exposed N-terminal amine. Alternatively, PNAs can be modified after synthesis by coupling to an introduced lysine or cysteine. The ease with which PNAs can be modified facilitates optimization for better solubility or for specific functional requirements. Once synthesized, the identity of PNAs and their derivatives can be confirmed by mass spectrometry. Several studies have made and  
20 utilized modifications of PNAs (for example, Norton *et al.*, Bioorg Med Chem. 1995 Apr;3(4):437-45; Petersen *et al.*, J Pept Sci. 1995 May-Jun;1(3):175-83; Orum *et al.*, Biotechniques. 1995 Sep;19(3):472-80; Footer *et al.*, Biochemistry. 1996 Aug 20;35(33):10673-9; Griffith *et al.*, Nucleic Acids Res. 1995 Aug 11;23(15):3003-8; Pardridge *et al.*, Proc Natl Acad Sci U S A. 1995 Jun 6;92(12):5592-6; Boffa *et al.*,  
25 Proc Natl Acad Sci U S A. 1995 Mar 14;92(6):1901-5; Gambacorti-Passerini *et al.*, Blood. 1996 Aug 15;88(4):1411-7; Armitage *et al.*, Proc Natl Acad Sci U S A. 1997 Nov 11;94(23):12320-5; Seeger *et al.*, Biotechniques. 1997 Sep;23(3):512-7). U.S. Patent No. 5,700,922 discusses PNA-DNA-PNA chimeric molecules and their uses in diagnostics, modulating protein in organisms, and treatment of conditions susceptible to  
30 therapeutics.

Methods of characterizing the antisense binding properties of PNAs are discussed in Rose (Anal Chem. 1993 Dec 15;65(24):3545-9) and Jensen *et al.* (Biochemistry. 1997 Apr 22;36(16):5072-7). Rose uses capillary gel electrophoresis to determine binding of PNAs to their complementary oligonucleotide, measuring the relative binding kinetics and stoichiometry. Similar types of measurements were made by Jensen *et al.* using BIAcore™ technology.

Other applications of PNAs that have been described and will be apparent to the skilled artisan include use in DNA strand invasion, antisense inhibition, mutational analysis, enhancers of transcription, nucleic acid purification, isolation of transcriptionally active genes, blocking of transcription factor binding, genome cleavage, biosensors, *in situ* hybridization, and the like.

#### Polynucleotide Identification, Characterization and Expression

Polynucleotide compositions of the present invention may be identified, prepared and/or manipulated using any of a variety of well established techniques (see generally, Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989, and other like references). For example, a polynucleotide may be identified, as described in more detail below, by screening a microarray of cDNAs for tumor-associated expression (*i.e.*, expression that is at least two fold greater in a tumor than in normal tissue, as determined using a representative assay provided herein). Such screens may be performed, for example, using the microarray technology of Affymetrix, Inc. (Santa Clara, CA) according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA* 93:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA* 94:2150-2155, 1997). Alternatively, polynucleotides may be amplified from cDNA prepared from cells expressing the proteins described herein, such as tumor cells.

Many template dependent processes are available to amplify a target sequences of interest present in a sample. One of the best known amplification methods is the polymerase chain reaction (PCR™) which is described in detail in U.S. Patent Nos. 4,683,195, 4,683,202 and 4,800,159, each of which is incorporated herein by

reference in its entirety. Briefly, in PCR™, two primer sequences are prepared which are complementary to regions on opposite complementary strands of the target sequence. An excess of deoxynucleoside triphosphates is added to a reaction mixture along with a DNA polymerase (*e.g.*, *Taq* polymerase). If the target sequence is present  
5 in a sample, the primers will bind to the target and the polymerase will cause the primers to be extended along the target sequence by adding on nucleotides. By raising and lowering the temperature of the reaction mixture, the extended primers will dissociate from the target to form reaction products, excess primers will bind to the target and to the reaction product and the process is repeated. Preferably reverse  
10 transcription and PCR™ amplification procedure may be performed in order to quantify the amount of mRNA amplified. Polymerase chain reaction methodologies are well known in the art.

Any of a number of other template dependent processes, many of which are variations of the PCR™ amplification technique, are readily known and available in  
15 the art. Illustratively, some such methods include the ligase chain reaction (referred to as LCR), described, for example, in Eur. Pat. Appl. Publ. No. 320,308 and U.S. Patent No. 4,883,750; Qbeta Replicase, described in PCT Intl. Pat. Appl. Publ. No. PCT/US87/00880; Strand Displacement Amplification (SDA) and Repair Chain Reaction (RCR). Still other amplification methods are described in Great Britain Pat.  
20 Appl. No. 2 202 328, and in PCT Intl. Pat. Appl. Publ. No. PCT/US89/01025. Other nucleic acid amplification procedures include transcription-based amplification systems (TAS) (PCT Intl. Pat. Appl. Publ. No. WO 88/10315), including nucleic acid sequence based amplification (NASBA) and 3SR. Eur. Pat. Appl. Publ. No. 329,822 describes a nucleic acid amplification process involving cyclically synthesizing single-stranded  
25 RNA ("ssRNA"), ssDNA, and double-stranded DNA (dsDNA). PCT Intl. Pat. Appl. Publ. No. WO 89/06700 describes a nucleic acid sequence amplification scheme based on the hybridization of a promoter/primer sequence to a target single-stranded DNA ("ssDNA") followed by transcription of many RNA copies of the sequence. Other amplification methods such as "RACE" (Frohman, 1990), and "one-sided PCR" (Ohara,  
30 1989) are also well-known to those of skill in the art.

An amplified portion of a polynucleotide of the present invention may be used to isolate a full length gene from a suitable library (e.g., a tumor cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide probes or primers suitable for amplification.

5 Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (e.g., by nick-translation or end-labeling with <sup>32</sup>P) using well known techniques. A bacterial or

10 bacteriophage library is then generally screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (see Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may

15 be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences can

20 then assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

Alternatively, amplification techniques, such as those described above, can be useful for obtaining a full length coding sequence from a partial cDNA sequence. One such amplification technique is inverse PCR (see Triglia et al., *Nucl. Acids Res.*

25 16:8186, 1988), which uses restriction enzymes to generate a fragment in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by amplification with a primer to a linker sequence and a primer specific to a

30 known region. The amplified sequences are typically subjected to a second round of

amplification with the same linker primer and a second primer specific to the known region. A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Another such technique is known as "rapid amplification of cDNA ends" or RACE. This technique involves the use of an internal primer and an external primer, which hybridizes to a polyA region or vector sequence, to identify sequences that are 5' and 3' of a known sequence. Additional techniques include capture PCR (Lagerstrom et al., *PCR Methods Applic. 1*:111-19, 1991) and walking PCR (Parker et al., *Nucl. Acids. Res. 19*:3055-60, 1991). Other methods employing amplification may also be employed to obtain a full length cDNA sequence.

In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (e.g., NCBI BLAST searches), and such ESTs may be used to generate a contiguous full length sequence. Full length DNA sequences may also be obtained by analysis of genomic fragments.

In other embodiments of the invention, polynucleotide sequences or fragments thereof which encode polypeptides of the invention, or fusion proteins or functional equivalents thereof, may be used in recombinant DNA molecules to direct expression of a polypeptide in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences that encode substantially the same or a functionally equivalent amino acid sequence may be produced and these sequences may be used to clone and express a given polypeptide.

As will be understood by those of skill in the art, it may be advantageous in some instances to produce polypeptide-encoding nucleotide sequences possessing non-naturally occurring codons. For example, codons preferred by a particular prokaryotic or eukaryotic host can be selected to increase the rate of protein expression or to produce a recombinant RNA transcript having desirable properties, such as a half-life which is longer than that of a transcript generated from the naturally occurring sequence.

Moreover, the polynucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter polypeptide encoding sequences for a variety of reasons, including but not limited to, alterations which modify the cloning, processing, and/or expression of the gene product. For example, DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. In addition, site-directed mutagenesis may be used to insert new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, or introduce mutations, and so forth.

10 In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences may be ligated to a heterologous sequence to encode a fusion protein. For example, to screen peptide libraries for inhibitors of polypeptide activity, it may be useful to encode a chimeric protein that can be recognized by a commercially available antibody. A fusion protein may also be engineered to contain a cleavage site located between the polypeptide-encoding sequence and the heterologous protein sequence, so that the polypeptide may be cleaved and purified away from the heterologous moiety.

Sequences encoding a desired polypeptide may be synthesized, in whole or in part, using chemical methods well known in the art (see Caruthers, M. H. et al. 20 (1980) *Nucl. Acids Res. Symp. Ser.* 215-223, Horn, T. et al. (1980) *Nucl. Acids Res. Symp. Ser.* 225-232). Alternatively, the protein itself may be produced using chemical methods to synthesize the amino acid sequence of a polypeptide, or a portion thereof. For example, peptide synthesis can be performed using various solid-phase techniques (Roberge, J. Y. et al. (1995) *Science* 269:202-204) and automated synthesis may be achieved, for example, using the ABI 431A Peptide Synthesizer (Perkin Elmer, Palo Alto, CA).

A newly synthesized peptide may be substantially purified by preparative high performance liquid chromatography (e.g., Creighton, T. (1983) *Proteins, Structures and Molecular Principles*, WH Freeman and Co., New York, N.Y.) or other comparable techniques available in the art. The composition of the synthetic peptides may be

confirmed by amino acid analysis or sequencing (e.g., the Edman degradation procedure). Additionally, the amino acid sequence of a polypeptide, or any part thereof, may be altered during direct synthesis and/or combined using chemical methods with sequences from other proteins, or any part thereof, to produce a variant polypeptide.

5           In order to express a desired polypeptide, the nucleotide sequences encoding the polypeptide, or functional equivalents, may be inserted into appropriate expression vector, *i.e.*, a vector which contains the necessary elements for the transcription and translation of the inserted coding sequence. Methods which are well known to those skilled in the art may be used to construct expression vectors containing  
10 sequences encoding a polypeptide of interest and appropriate transcriptional and translational control elements. These methods include *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. Such techniques are described, for example, in Sambrook, J. et al. (1989) *Molecular Cloning, A Laboratory Manual*, Cold Spring Harbor Press, Plainview, N.Y., and Ausubel, F. M. et al. (1989) *Current Protocols in Molecular Biology*, John Wiley & Sons, New York.  
15 N.Y.

A variety of expression vector/host systems may be utilized to contain and express polynucleotide sequences. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid,  
20 or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with virus expression vectors (e.g., baculovirus); plant cell systems transformed with virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or animal cell systems.

25           The "control elements" or "regulatory sequences" present in an expression vector are those non-translated regions of the vector--enhancers, promoters, 5' and 3' untranslated regions--which interact with host cellular proteins to carry out transcription and translation. Such elements may vary in their strength and specificity. Depending on the vector system and host utilized, any number of suitable transcription  
30 and translation elements, including constitutive and inducible promoters, may be used.



For example, when cloning in bacterial systems, inducible promoters such as the hybrid lacZ promoter of the PBLUESCRIPT phagemid (Stratagene, La Jolla, Calif.) or PSPORT1 plasmid (Gibco BRL, Gaithersburg, MD) and the like may be used. In mammalian cell systems, promoters from mammalian genes or from mammalian viruses  
5 are generally preferred. If it is necessary to generate a cell line that contains multiple copies of the sequence encoding a polypeptide, vectors based on SV40 or EBV may be advantageously used with an appropriate selectable marker.

In bacterial systems, any of a number of expression vectors may be selected depending upon the use intended for the expressed polypeptide. For example,  
10 when large quantities are needed, for example for the induction of antibodies, vectors which direct high level expression of fusion proteins that are readily purified may be used. Such vectors include, but are not limited to, the multifunctional *E. coli* cloning and expression vectors such as BLUESCRIPT (Stratagene), in which the sequence encoding the polypeptide of interest may be ligated into the vector in frame with  
15 sequences for the amino-terminal Met and the subsequent 7 residues of .beta.-galactosidase so that a hybrid protein is produced; pIN vectors (Van Heeke, G. and S. M. Schuster (1989) *J. Biol. Chem.* 264:5503-5509); and the like. pGEX Vectors (Promega, Madison, Wis.) may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are  
20 soluble and can easily be purified from lysed cells by adsorption to glutathione-agarose beads followed by elution in the presence of free glutathione. Proteins made in such systems may be designed to include heparin, thrombin, or factor XA protease cleavage sites so that the cloned polypeptide of interest can be released from the GST moiety at will.

25 In the yeast, *Saccharomyces cerevisiae*, a number of vectors containing constitutive or inducible promoters such as alpha factor, alcohol oxidase, and PGH may be used. For reviews, see Ausubel et al. (supra) and Grant et al. (1987) *Methods Enzymol.* 153:516-544.

In cases where plant expression vectors are used, the expression of  
30 sequences encoding polypeptides may be driven by any of a number of promoters. For

example, viral promoters such as the 35S and 19S promoters of CaMV may be used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) *EMBO J.* 6:307-311. Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used (Coruzzi, G. et al. (1984) *EMBO J.* 3:1671-1680; Broglie, R. et al. (1984) *Science* 224:838-843; and Winter, J. et al. (1991) *Results Probl. Cell Differ.* 17:85-105). These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. Such techniques are described in a number of generally available reviews (see, for example, Hobbs, S. or Murry, L. E. in McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York, N.Y.; pp. 191-196).

An insect system may also be used to express a polypeptide of interest. For example, in one such system, Autographa californica nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes in *Spodoptera frugiperda* cells or in *Trichoplusia* larvae. The sequences encoding the polypeptide may be cloned into a non-essential region of the virus, such as the polyhedrin gene, and placed under control of the polyhedrin promoter. Successful insertion of the polypeptide-encoding sequence will render the polyhedrin gene inactive and produce recombinant virus lacking coat protein. The recombinant viruses may then be used to infect, for example, *S. frugiperda* cells or *Trichoplusia* larvae in which the polypeptide of interest may be expressed (Engelhard, E. K. et al. (1994) *Proc. Natl. Acad. Sci.* 91:3224-3227).

In mammalian host cells, a number of viral-based expression systems are generally available. For example, in cases where an adenovirus is used as an expression vector, sequences encoding a polypeptide of interest may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain a viable virus which is capable of expressing the polypeptide in infected host cells (Logan, J. and Shenk, T. (1984) *Proc. Natl. Acad. Sci.* 81:3655-3659). In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells.

Specific initiation signals may also be used to achieve more efficient translation of sequences encoding a polypeptide of interest. Such signals include the ATG initiation codon and adjacent sequences. In cases where sequences encoding the polypeptide, its initiation codon, and upstream sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a portion thereof, is inserted, exogenous translational control signals including the ATG initiation codon should be provided. Furthermore, the initiation codon should be in the correct reading frame to ensure translation of the entire insert. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers which are appropriate for the particular cell system which is used, such as those described in the literature (Scharf, D. et al. (1994) *Results Probl. Cell Differ.* 20:125-162).

In addition, a host cell strain may be chosen for its ability to modulate the expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" form of the protein may also be used to facilitate correct insertion, folding and/or function. Different host cells such as CHO, COS, HeLa, MDCK, HEK293, and WI38, which have specific cellular machinery and characteristic mechanisms for such post-translational activities, may be chosen to ensure the correct modification and processing of the foreign protein.

For long-term, high-yield production of recombinant proteins, stable expression is generally preferred. For example, cell lines which stably express a polynucleotide of interest may be transformed using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for 1-2 days in an enriched media before they are switched to selective media. The purpose of the selectable marker is to confer resistance to selection, and its presence allows growth and recovery of cells which

successfully express the introduced sequences. Resistant clones of stably transformed cells may be proliferated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase (Wigler, M. et al. (1977) *Cell* 11:223-32) and adenine phosphoribosyltransferase (Lowy, I. et al. (1990) *Cell* 22:817-23) genes which can be employed in tk.sup.- or aprt.sup.- cells, respectively. Also, antimetabolite, antibiotic or herbicide resistance can be used as the basis for selection; for example, dhfr which confers resistance to methotrexate (Wigler, M. et al. (1980) *Proc. Natl. Acad. Sci.* 77:3567-70); npt, which confers resistance to the aminoglycosides, neomycin and G-418 (Colbere-Garapin, F. et al (1981) *J. Mol. Biol.* 150:1-14); and als or pat, which confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively (Murry, *supra*). Additional selectable genes have been described, for example, trpB, which allows cells to utilize indole in place of tryptophan, or hisD, which allows cells to utilize histinol in place of histidine (Hartman, S. C. and R. C. Mulligan (1988) *Proc. Natl. Acad. Sci.* 85:8047-51). The use of visible markers has gained popularity with such markers as anthocyanins, beta-glucuronidase and its substrate GUS, and luciferase and its substrate luciferin, being widely used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system (Rhodes, C. A. et al. (1995) *Methods Mol. Biol.* 55:121-131).

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, its presence and expression may need to be confirmed. For example, if the sequence encoding a polypeptide is inserted within a marker gene sequence, recombinant cells containing sequences can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a polypeptide-encoding sequence under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

Alternatively, host cells that contain and express a desired polynucleotide sequence may be identified by a variety of procedures known to those of

skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations and protein bioassay or immunoassay techniques which include, for example, membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein.

5           A variety of protocols for detecting and measuring the expression of polynucleotide-encoded products, using either polyclonal or monoclonal antibodies specific for the product are known in the art. Examples include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal  
10 antibodies reactive to two non-interfering epitopes on a given polypeptide may be preferred for some applications, but a competitive binding assay may also be employed. These and other assays are described, among other places, in Hampton, R. et al. (1990; *Serological Methods, a Laboratory Manual*, APS Press, St Paul, Minn.) and Maddox, D. E. et al. (1983; *J. Exp. Med.* 158:1211-1216).

15           A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides include oligolabeling, nick translation, end-labeling or PCR amplification using a labeled nucleotide. Alternatively, the sequences, or any portions  
20 thereof may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits. Suitable reporter molecules or labels, which may be used  
25 include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with a polynucleotide sequence of interest may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a recombinant cell may be secreted or contained  
30 intracellularly depending on the sequence and/or the vector used. As will be understood

by those of skill in the art, expression vectors containing polynucleotides of the invention may be designed to contain signal sequences which direct secretion of the encoded polypeptide through a prokaryotic or eukaryotic cell membrane. Other recombinant constructions may be used to join sequences encoding a polypeptide of interest to nucleotide sequence encoding a polypeptide domain which will facilitate purification of soluble proteins. Such purification facilitating domains include, but are not limited to, metal chelating peptides such as histidine-tryptophan modules that allow purification on immobilized metals, protein A domains that allow purification on immobilized immunoglobulin, and the domain utilized in the FLAGS extension/affinity purification system (Immunex Corp., Seattle, Wash.). The inclusion of cleavable linker sequences such as those specific for Factor XA or enterokinase (Invitrogen, San Diego, Calif.) between the purification domain and the encoded polypeptide may be used to facilitate purification. One such expression vector provides for expression of a fusion protein containing a polypeptide of interest and a nucleic acid encoding 6 histidine residues preceding a thioredoxin or an enterokinase cleavage site. The histidine residues facilitate purification on IMIAC (immobilized metal ion affinity chromatography) as described in Porath, J. et al. (1992, *Prot. Exp. Purif.* 3:263-281) while the enterokinase cleavage site provides a means for purifying the desired polypeptide from the fusion protein. A discussion of vectors which contain fusion proteins is provided in Kroll, D. J. et al. (1993; *DNA Cell Biol.* 12:441-453).

In addition to recombinant production methods, polypeptides of the invention, and fragments thereof, may be produced by direct peptide synthesis using solid-phase techniques (Merrifield J. (1963) *J. Am. Chem. Soc.* 85:2149-2154). Protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be achieved, for example, using Applied Biosystems 431A Peptide Synthesizer (Perkin Elmer). Alternatively, various fragments may be chemically synthesized separately and combined using chemical methods to produce the full length molecule.

Antibody Compositions, Fragments Thereof and Other Binding Agents

According to another aspect, the present invention further provides binding agents, such as antibodies and antigen-binding fragments thereof, that exhibit immunological binding to a tumor polypeptide disclosed herein, or to a portion, variant  
5 or derivative thereof. An antibody, or antigen-binding fragment thereof, is said to "specifically bind," "immunologically bind," and/or is "immunologically reactive" to a polypeptide of the invention if it reacts at a detectable level (within, for example, an ELISA assay) with the polypeptide, and does not react detectably with unrelated polypeptides under similar conditions.

10 Immunological binding, as used in this context, generally refers to the non-covalent interactions of the type which occur between an immunoglobulin molecule and an antigen for which the immunoglobulin is specific. The strength, or affinity of immunological binding interactions can be expressed in terms of the dissociation constant ( $K_d$ ) of the interaction, wherein a smaller  $K_d$  represents a greater  
15 affinity. Immunological binding properties of selected polypeptides can be quantified using methods well known in the art. One such method entails measuring the rates of antigen-binding site/antigen complex formation and dissociation, wherein those rates depend on the concentrations of the complex partners, the affinity of the interaction, and on geometric parameters that equally influence the rate in both directions. Thus, both  
20 the "on rate constant" ( $K_{on}$ ) and the "off rate constant" ( $K_{off}$ ) can be determined by calculation of the concentrations and the actual rates of association and dissociation. The ratio of  $K_{off}/K_{on}$  enables cancellation of all parameters not related to affinity, and is thus equal to the dissociation constant  $K_d$ . See, generally, Davies et al. (1990) Annual Rev. Biochem. 59:439-473.

25 An "antigen-binding site," or "binding portion" of an antibody refers to the part of the immunoglobulin molecule that participates in antigen binding. The antigen binding site is formed by amino acid residues of the N-terminal variable ("V") regions of the heavy ("H") and light ("L") chains. Three highly divergent stretches within the V regions of the heavy and light chains are referred to as "hypervariable  
30 regions" which are interposed between more conserved flanking stretches known as

"framework regions," or "FRs". Thus the term "FR" refers to amino acid sequences which are naturally found between and adjacent to hypervariable regions in immunoglobulins. In an antibody molecule, the three hypervariable regions of a light chain and the three hypervariable regions of a heavy chain are disposed relative to each other in three dimensional space to form an antigen-binding surface. The antigen-binding surface is complementary to the three-dimensional surface of a bound antigen, and the three hypervariable regions of each of the heavy and light chains are referred to as "complementarity-determining regions," or "CDRs."

Binding agents may be further capable of differentiating between patients with and without a cancer, such as prostate cancer, using the representative assays provided herein. For example, antibodies or other binding agents that bind to a tumor protein will preferably generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, more preferably at least about 30% of patients. Alternatively, or in addition, the antibody will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies this requirement, biological samples (*e.g.*, blood, sera, sputum, urine and/or tumor biopsies) from patients with and without a cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. Preferably, a statistically significant number of samples with and without the disease will be assayed. Each binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. *See, e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In general, antibodies can be produced by cell culture techniques, including the generation



of monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (e.g., mice, rats, rabbits, sheep or goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol.* 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (i.e., reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

A number of therapeutically useful molecules are known in the art which comprise antigen-binding sites that are capable of exhibiting immunological binding properties of an antibody molecule. The proteolytic enzyme papain preferentially cleaves IgG molecules to yield several fragments, two of which (the "F(ab)" fragments) each comprise a covalent heterodimer that includes an intact antigen-binding site. The enzyme pepsin is able to cleave IgG molecules to provide several fragments, including the "F(ab')<sub>2</sub>" fragment which comprises both antigen-binding sites. An "Fv" fragment can be produced by preferential proteolytic cleavage of an IgM, and on rare occasions IgG or IgA immunoglobulin molecule. Fv fragments are, however, more commonly derived using recombinant techniques known in the art. The Fv fragment includes a non-covalent V<sub>H</sub>::V<sub>L</sub> heterodimer including an antigen-binding site which retains much of the antigen recognition and binding capabilities of the native antibody molecule. Inbar et al. (1972) Proc. Nat. Acad. Sci. USA 69:2659-2662; Hochman et al. (1976) Biochem 15:2706-2710; and Ehrlich et al. (1980) Biochem 19:4091-4096.

A single chain Fv ("sFv") polypeptide is a covalently linked V<sub>H</sub>::V<sub>L</sub> heterodimer which is expressed from a gene fusion including V<sub>H</sub>- and V<sub>L</sub>-encoding genes linked by a peptide-encoding linker. Huston et al. (1988) Proc. Nat. Acad. Sci. USA 85(16):5879-5883. A number of methods have been described to discern chemical structures for converting the naturally aggregated--but chemically separated--light and heavy polypeptide chains from an antibody V region into an sFv molecule which will fold into a three dimensional structure substantially similar to the structure of an

antigen-binding site. See, *e.g.*, U.S. Pat. Nos. 5,091,513 and 5,132,405, to Huston et al.; and U.S. Pat. No. 4,946,778, to Ladner et al.

Each of the above-described molecules includes a heavy chain and a light chain CDR set, respectively interposed between a heavy chain and a light chain FR set which provide support to the CDRs and define the spatial relationship of the CDRs relative to each other. As used herein, the term "CDR set" refers to the three hypervariable regions of a heavy or light chain V region. Proceeding from the N-terminus of a heavy or light chain, these regions are denoted as "CDR1," "CDR2," and "CDR3" respectively. An antigen-binding site, therefore, includes six CDRs, comprising the CDR set from each of a heavy and a light chain V region. A polypeptide comprising a single CDR, (*e.g.*, a CDR1, CDR2 or CDR3) is referred to herein as a "molecular recognition unit." Crystallographic analysis of a number of antigen-antibody complexes has demonstrated that the amino acid residues of CDRs form extensive contact with bound antigen, wherein the most extensive antigen contact is with the heavy chain CDR3. Thus, the molecular recognition units are primarily responsible for the specificity of an antigen-binding site.

As used herein, the term "FR set" refers to the four flanking amino acid sequences which frame the CDRs of a CDR set of a heavy or light chain V region. Some FR residues may contact bound antigen; however, FRs are primarily responsible for folding the V region into the antigen-binding site, particularly the FR residues directly adjacent to the CDRs. Within FRs, certain amino residues and certain structural features are very highly conserved. In this regard, all V region sequences contain an internal disulfide loop of around 90 amino acid residues. When the V regions fold into a binding-site, the CDRs are displayed as projecting loop motifs which form an antigen-binding surface. It is generally recognized that there are conserved structural regions of FRs which influence the folded shape of the CDR loops into certain "canonical" structures—regardless of the precise CDR amino acid sequence. Further, certain FR residues are known to participate in non-covalent interdomain contacts which stabilize the interaction of the antibody heavy and light chains.

A number of "humanized" antibody molecules comprising an antigen-binding site derived from a non-human immunoglobulin have been described, including chimeric antibodies having rodent V regions and their associated CDRs fused to human constant domains (Winter et al. (1991) Nature 349:293-299; Lobuglio et al. (1989) Proc. Nat. Acad. Sci. USA 86:4220-4224; Shaw et al. (1987) J Immunol. 138:4534-4538; and Brown et al. (1987) Cancer Res. 47:3577-3583), rodent CDRs grafted into a human supporting FR prior to fusion with an appropriate human antibody constant domain (Riechmann et al. (1988) Nature 332:323-327; Verhoeven et al. (1988) Science 239:1534-1536; and Jones et al. (1986) Nature 321:522-525), and rodent CDRs supported by recombinantly veneered rodent FRs (European Patent Publication No. 519,596, published Dec. 23, 1992). These "humanized" molecules are designed to minimize unwanted immunological response toward rodent antihuman antibody molecules which limits the duration and effectiveness of therapeutic applications of those moieties in human recipients.

As used herein, the terms "veneered FRs" and "recombinantly veneered FRs" refer to the selective replacement of FR residues from, *e.g.*, a rodent heavy or light chain V region, with human FR residues in order to provide a xenogeneic molecule comprising an antigen-binding site which retains substantially all of the native FR polypeptide folding structure. Veneering techniques are based on the understanding that the ligand binding characteristics of an antigen-binding site are determined primarily by the structure and relative disposition of the heavy and light chain CDR sets within the antigen-binding surface. Davies et al. (1990) Ann. Rev. Biochem. 59:439-473. Thus, antigen binding specificity can be preserved in a humanized antibody only wherein the CDR structures, their interaction with each other, and their interaction with the rest of the V region domains are carefully maintained. By using veneering techniques, exterior (*e.g.*, solvent-accessible) FR residues which are readily encountered by the immune system are selectively replaced with human residues to provide a hybrid molecule that comprises either a weakly immunogenic, or substantially non-immunogenic veneered surface.

The process of veneering makes use of the available sequence data for human antibody variable domains compiled by Kabat et al., in Sequences of Proteins of Immunological Interest, 4th ed., (U.S. Dept. of Health and Human Services, U.S. Government Printing Office, 1987), updates to the Kabat database, and other accessible U.S. and foreign databases (both nucleic acid and protein). Solvent accessibilities of V region amino acids can be deduced from the known three-dimensional structure for human and murine antibody fragments. There are two general steps in veneering a murine antigen-binding site. Initially, the FRs of the variable domains of an antibody molecule of interest are compared with corresponding FR sequences of human variable domains obtained from the above-identified sources. The most homologous human V regions are then compared residue by residue to corresponding murine amino acids. The residues in the murine FR which differ from the human counterpart are replaced by the residues present in the human moiety using recombinant techniques well known in the art. Residue switching is only carried out with moieties which are at least partially exposed (solvent accessible), and care is exercised in the replacement of amino acid residues which may have a significant effect on the tertiary structure of V region domains, such as proline, glycine and charged amino acids.

In this manner, the resultant "veneered" murine antigen-binding sites are thus designed to retain the murine CDR residues, the residues substantially adjacent to the CDRs, the residues identified as buried or mostly buried (solvent inaccessible), the residues believed to participate in non-covalent (e.g., electrostatic and hydrophobic) contacts between heavy and light chain domains, and the residues from conserved structural regions of the FRs which are believed to influence the "canonical" tertiary structures of the CDR loops. These design criteria are then used to prepare recombinant nucleotide sequences which combine the CDRs of both the heavy and light chain of a murine antigen-binding site into human-appearing FRs that can be used to transfect mammalian cells for the expression of recombinant human antibodies which exhibit the antigen specificity of the murine antibody molecule.

In another embodiment of the invention, monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in

this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include  $^{90}\text{Y}$ ,  $^{123}\text{I}$ ,  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{211}\text{At}$ , and  $^{212}\text{Bi}$ . Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred  
5 toxins include ricin, abrin, diphtheria toxin, cholera toxin, gelonin, *Pseudomonas* exotoxin, *Shigella* toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (*e.g.*, covalently bonded) to a suitable monoclonal antibody either directly or indirectly (*e.g.*, via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a  
10 substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (*e.g.*, a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an  
15 antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which  
20 otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups,  
25 sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, *e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of  
30 different cleavable linker groups have been described. The mechanisms for the

intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (*e.g.*, U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (*e.g.*, U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of derivatized amino acid side chains (*e.g.*, U.S. Patent No. 4,638,045, to Kohn et al.), by  
5 serum complement-mediated hydrolysis (*e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (*e.g.*, U.S. Patent No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody.  
10 Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers that provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent  
15 bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (*e.g.*, U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (*e.g.*, U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (*e.g.*, U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for  
20 radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For  
25 example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

### T Cell Compositions

The present invention, in another aspect, provides T cells specific for a tumor polypeptide disclosed herein, or for a variant or derivative thereof. Such cells

may generally be prepared *in vitro* or *ex vivo*, using standard procedures. For example, T cells may be isolated from bone marrow, peripheral blood, or a fraction of bone marrow or peripheral blood of a patient, using a commercially available cell separation system, such as the Isolex™ System, available from Nexell Therapeutics, Inc. (Irvine, CA; see also U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). Alternatively, T cells may be derived from related or unrelated humans, non-human mammals, cell lines or cultures.

T cells may be stimulated with a polypeptide, polynucleotide encoding a polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide of interest. Preferably, a tumor polypeptide or polynucleotide of the invention is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

T cells are considered to be specific for a polypeptide of the present invention if the T cells specifically proliferate, secrete cytokines or kill target cells coated with the polypeptide or expressing a gene encoding the polypeptide. T cell specificity may be evaluated using any of a variety of standard techniques. For example, within a chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen et al., *Cancer Res.* 54:1065-1070, 1994. Alternatively, detection of the proliferation of T cells may be accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased rate of DNA synthesis (*e.g.*, by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with a tumor polypeptide (100 ng/ml - 100 µg/ml, preferably 200 ng/ml - 25 µg/ml) for 3 - 7 days will typically result in at least a two fold increase in proliferation of the T cells. Contact as described above for 2-3 hours should result in activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (*e.g.*, TNF or IFN-γ) is indicative of T cell activation (*see* Coligan et



al., Current Protocols in Immunology, vol. 1, Wiley Interscience (Greene 1998)). T cells that have been activated in response to a tumor polypeptide, polynucleotide or polypeptide-expressing APC may be CD4<sup>+</sup> and/or CD8<sup>+</sup>. Tumor polypeptide-specific T cells may be expanded using standard techniques. Within preferred embodiments, the T cells are derived from a patient, a related donor or an unrelated donor, and are administered to the patient following stimulation and expansion.

For therapeutic purposes, CD4<sup>+</sup> or CD8<sup>+</sup> T cells that proliferate in response to a tumor polypeptide, polynucleotide or APC can be expanded in number either *in vitro* or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a variety of ways. For example, the T cells can be re-exposed to a tumor polypeptide, or a short peptide corresponding to an immunogenic portion of such a polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize a tumor polypeptide. Alternatively, one or more T cells that proliferate in the presence of the tumor polypeptide can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution.

#### Pharmaceutical Compositions

In additional embodiments, the present invention concerns formulation of one or more of the polynucleotide, polypeptide, T-cell and/or antibody compositions disclosed herein in pharmaceutically-acceptable carriers for administration to a cell or an animal, either alone, or in combination with one or more other modalities of therapy.

It will be understood that, if desired, a composition as disclosed herein may be administered in combination with other agents as well, such as, *e.g.*, other proteins or polypeptides or various pharmaceutically-active agents. In fact, there is virtually no limit to other components that may also be included, given that the additional agents do not cause a significant adverse effect upon contact with the target cells or host tissues. The compositions may thus be delivered along with various other agents as required in the particular instance. Such compositions may be purified from host cells or other biological sources, or alternatively may be chemically synthesized as

described herein. Likewise, such compositions may further comprise substituted or derivatized RNA or DNA compositions.

Therefore, in another aspect of the present invention, pharmaceutical compositions are provided comprising one or more of the polynucleotide, polypeptide, antibody, and/or T-cell compositions described herein in combination with a physiologically acceptable carrier. In certain preferred embodiments, the pharmaceutical compositions of the invention comprise immunogenic polynucleotide and/or polypeptide compositions of the invention for use in prophylactic and therapeutic vaccine applications. Vaccine preparation is generally described in, for example, M.F. Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Generally, such compositions will comprise one or more polynucleotide and/or polypeptide compositions of the present invention in combination with one or more immunostimulants.

It will be apparent that any of the pharmaceutical compositions described herein can contain pharmaceutically acceptable salts of the polynucleotides and polypeptides of the invention. Such salts can be prepared, for example, from pharmaceutically acceptable non-toxic bases, including organic bases (e.g., salts of primary, secondary and tertiary amines and basic amino acids) and inorganic bases (e.g., sodium, potassium, lithium, ammonium, calcium and magnesium salts).

In another embodiment, illustrative immunogenic compositions, e.g., vaccine compositions, of the present invention comprise DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated *in situ*. As noted above, the polynucleotide may be administered within any of a variety of delivery systems known to those of ordinary skill in the art. Indeed, numerous gene delivery techniques are well known in the art, such as those described by Rolland, *Crit. Rev. Therap. Drug Carrier Systems* 15:143-198, 1998, and references cited therein. Appropriate polynucleotide expression systems will, of course, contain the necessary regulatory DNA regulatory sequences for expression in a patient (such as a suitable promoter and terminating signal). Alternatively, bacterial delivery systems may involve

the administration of a bacterium (such as *Bacillus-Calmette-Guerrin*) that expresses an immunogenic portion of the polypeptide on its cell surface or secretes such an epitope.

Therefore, in certain embodiments, polynucleotides encoding immunogenic polypeptides described herein are introduced into suitable mammalian host cells for expression using any of a number of known viral-based systems. In one illustrative embodiment, retroviruses provide a convenient and effective platform for gene delivery systems. A selected nucleotide sequence encoding a polypeptide of the present invention can be inserted into a vector and packaged in retroviral particles using techniques known in the art. The recombinant virus can then be isolated and delivered to a subject. A number of illustrative retroviral systems have been described (e.g., U.S. Pat. No. 5,219,740; Miller and Rosman (1989) *BioTechniques* 7:980-990; Miller, A. D. (1990) *Human Gene Therapy* 1:5-14; Scarpa et al. (1991) *Virology* 180:849-852; Burns et al. (1993) *Proc. Natl. Acad. Sci. USA* 90:8033-8037; and Boris-Lawrie and Temin (1993) *Cur. Opin. Genet. Develop.* 3:102-109.

In addition, a number of illustrative adenovirus-based systems have also been described. Unlike retroviruses which integrate into the host genome, adenoviruses persist extrachromosomally thus minimizing the risks associated with insertional mutagenesis (Haj-Ahmad and Graham (1986) *J. Virol.* 57:267-274; Bett et al. (1993) *J. Virol.* 67:5911-5921; Mittereder et al. (1994) *Human Gene Therapy* 5:717-729; Seth et al. (1994) *J. Virol.* 68:933-940; Barr et al. (1994) *Gene Therapy* 1:51-58; Berkner, K. L. (1988) *BioTechniques* 6:616-629; and Rich et al. (1993) *Human Gene Therapy* 4:461-476).

Various adeno-associated virus (AAV) vector systems have also been developed for polynucleotide delivery. AAV vectors can be readily constructed using techniques well known in the art. See, e.g., U.S. Pat. Nos. 5,173,414 and 5,139,941; International Publication Nos. WO 92/01070 and WO 93/03769; Lebkowski et al. (1988) *Molec. Cell. Biol.* 8:3988-3996; Vincent et al. (1990) *Vaccines 90* (Cold Spring Harbor Laboratory Press); Carter, B. J. (1992) *Current Opinion in Biotechnology* 3:533-539; Muzyczka, N. (1992) *Current Topics in Microbiol. and Immunol.* 158:97-129;

Kotin, R. M. (1994) Human Gene Therapy 5:793-801; Shelling and Smith (1994) Gene Therapy 1:165-169; and Zhou et al. (1994) J. Exp. Med. 179:1867-1875.

Additional viral vectors useful for delivering the polynucleotides encoding polypeptides of the present invention by gene transfer include those derived from the pox family of viruses, such as vaccinia virus and avian poxvirus. By way of example, vaccinia virus recombinants expressing the novel molecules can be constructed as follows. The DNA encoding a polypeptide is first inserted into an appropriate vector so that it is adjacent to a vaccinia promoter and flanking vaccinia DNA sequences, such as the sequence encoding thymidine kinase (TK). This vector is then used to transfect cells which are simultaneously infected with vaccinia. Homologous recombination serves to insert the vaccinia promoter plus the gene encoding the polypeptide of interest into the viral genome. The resulting TK<sup>sup</sup>(-) recombinant can be selected by culturing the cells in the presence of 5-bromodeoxyuridine and picking viral plaques resistant thereto.

A vaccinia-based infection/transfection system can be conveniently used to provide for inducible, transient expression or coexpression of one or more polypeptides described herein in host cells of an organism. In this particular system, cells are first infected in vitro with a vaccinia virus recombinant that encodes the bacteriophage T7 RNA polymerase. This polymerase displays exquisite specificity in that it only transcribes templates bearing T7 promoters. Following infection, cells are transfected with the polynucleotide or polynucleotides of interest, driven by a T7 promoter. The polymerase, expressed in the cytoplasm from the vaccinia virus recombinant transcribes the transfected DNA into RNA which is then translated into polypeptide by the host translational machinery. The method provides for high level, transient, cytoplasmic production of large quantities of RNA and its translation products. See, e.g., Elroy-Stein and Moss, Proc. Natl. Acad. Sci. USA (1990) 87:6743-6747; Fuerst et al. Proc. Natl. Acad. Sci. USA (1986) 83:8122-8126.

Alternatively, avipoxviruses, such as the fowlpox and canarypox viruses, can also be used to deliver the coding sequences of interest. Recombinant avipox viruses, expressing immunogens from mammalian pathogens, are known to confer

protective immunity when administered to non-avian species. The use of an Avipox vector is particularly desirable in human and other mammalian species since members of the Avipox genus can only productively replicate in susceptible avian species and therefore are not infective in mammalian cells. Methods for producing recombinant  
5 Avipoxviruses are known in the art and employ genetic recombination, as described above with respect to the production of vaccinia viruses. See, *e.g.*, WO 91/12882; WO 89/03429; and WO 92/03545.

Any of a number of alphavirus vectors can also be used for delivery of polynucleotide compositions of the present invention, such as those vectors described in  
10 U.S. Patent Nos. 5,843,723; 6,015,686; 6,008,035 and 6,015,694. Certain vectors based on Venezuelan Equine Encephalitis (VEE) can also be used, illustrative examples of which can be found in U.S. Patent Nos. 5,505,947 and 5,643,576.

Moreover, molecular conjugate vectors, such as the adenovirus chimeric vectors described in Michael et al. *J. Biol. Chem.* (1993) 268:6866-6869 and Wagner et  
15 al. *Proc. Natl. Acad. Sci. USA* (1992) 89:6099-6103, can also be used for gene delivery under the invention.

Additional illustrative information on these and other known viral-based delivery systems can be found, for example, in Fisher-Hoch et al., *Proc. Natl. Acad. Sci. USA* 86:317-321, 1989; Flexner et al., *Ann. N.Y. Acad. Sci.* 569:86-103, 1989; Flexner  
20 et al., *Vaccine* 8:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, *Biotechniques* 6:616-627, 1988; Rosenfeld et al., *Science* 252:431-434, 1991; Kolls et al., *Proc. Natl. Acad. Sci. USA* 91:215-219, 1994; Kass-Eisler et al., *Proc. Natl. Acad. Sci. USA* 90:11498-11502, 1993; Guzman et al.,  
25 *Circulation* 88:2838-2848, 1993; and Guzman et al., *Cir. Res.* 73:1202-1207, 1993.

In certain embodiments, a polynucleotide may be integrated into the genome of a target cell. This integration may be in a specific location and orientation via homologous recombination (gene replacement) or it may be integrated in a random, non-specific location (gene augmentation). In yet further embodiments, the  
30 polynucleotide may be stably maintained in the cell as a separate, episomal segment of

DNA. Such polynucleotide segments or "episomes" encode sequences sufficient to permit maintenance and replication independent of or in synchronization with the host cell cycle. The manner in which the expression construct is delivered to a cell and where in the cell the polynucleotide remains is dependent on the type of expression  
5 construct employed.

In another embodiment of the invention, a polynucleotide is administered/delivered as "naked" DNA, for example as described in Ulmer et al., *Science* 259:1745-1749, 1993 and reviewed by Cohen, *Science* 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable  
10 beads, which are efficiently transported into the cells.

In still another embodiment, a composition of the present invention can be delivered via a particle bombardment approach, many of which have been described. In one illustrative example, gas-driven particle acceleration can be achieved with devices such as those manufactured by Powderject Pharmaceuticals PLC (Oxford, UK)  
15 and Powderject Vaccines Inc. (Madison, WI), some examples of which are described in U.S. Patent Nos. 5,846,796; 6,010,478; 5,865,796; 5,584,807; and EP Patent No. 0500 799. This approach offers a needle-free delivery approach wherein a dry powder formulation of microscopic particles, such as polynucleotide or polypeptide particles, are accelerated to high speed within a helium gas jet generated by a hand held device,  
20 propelling the particles into a target tissue of interest.

In a related embodiment, other devices and methods that may be useful for gas-driven needle-less injection of compositions of the present invention include those provided by Bioject, Inc. (Portland, OR), some examples of which are described in U.S. Patent Nos. 4,790,824; 5,064,413; 5,312,335; 5,383,851; 5,399,163; 5,520,639  
25 and 5,993,412.

According to another embodiment, the pharmaceutical compositions described herein will comprise one or more immunostimulants in addition to the immunogenic polynucleotide, polypeptide, antibody, T-cell and/or APC compositions of this invention. An immunostimulant refers to essentially any substance that enhances  
30 or potentiates an immune response (antibody and/or cell-mediated) to an exogenous

antigen. One preferred type of immunostimulant comprises an adjuvant. Many adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune responses, such as lipid A, *Bordetella pertussis* or *Mycobacterium tuberculosis* derived proteins.

5 Certain adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI); Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ); AS-2 (SmithKline Beecham, Philadelphia, PA); aluminum salts such as aluminum hydroxide gel (alum) or aluminum phosphate; salts of calcium, iron or zinc; an insoluble suspension of acylated tyrosine; acylated

10 sugars; cationically or anionically derivatized polysaccharides; polyphosphazenes; biodegradable microspheres; monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF, interleukin-2, -7, -12, and other like growth factors, may also be used as adjuvants.

Within certain embodiments of the invention, the adjuvant composition

15 is preferably one that induces an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (*e.g.*, IFN- $\gamma$ , TNF $\alpha$ , IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (*e.g.*, IL-4, IL-5, IL-6 and IL-10) tend to favor the induction of humoral immune responses. Following application of a vaccine as

20 provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman,

25 *Ann. Rev. Immunol.* 7:145-173, 1989.

Certain preferred adjuvants for eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A, together with an aluminum salt. MPL<sup>®</sup> adjuvants are available from Corixa Corporation (Seattle, WA; *see*, for example, US

30 Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). CpG-containing

oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555, WO 99/33488 and U.S. Patent Nos. 6,008,200 and 5,856,462. Immunostimulatory DNA sequences are also described, for example, by

5 Sato et al., *Science* 273:352, 1996. Another preferred adjuvant comprises a saponin, such as Quil A, or derivatives thereof, including QS21 and QS7 (Aquila Biopharmaceuticals Inc., Framingham, MA); Escin; Digitonin; or *Gypsophila* or *Chenopodium quinoa* saponins. Other preferred formulations include more than one saponin in the adjuvant combinations of the present invention, for example

10 combinations of at least two of the following group comprising QS21, QS7, Quil A,  $\beta$ -escin, or digitonin.

Alternatively the saponin formulations may be combined with vaccine vehicles composed of chitosan or other polycationic polymers, polylactide and polylactide-co-glycolide particles, poly-N-acetyl glucosamine-based polymer matrix,

15 particles composed of polysaccharides or chemically modified polysaccharides, liposomes and lipid-based particles, particles composed of glycerol monoesters, etc. The saponins may also be formulated in the presence of cholesterol to form particulate structures such as liposomes or ISCOMs. Furthermore, the saponins may be formulated together with a polyoxyethylene ether or ester, in either a non-particulate solution or

20 suspension, or in a particulate structure such as a paucilamellar liposome or ISCOM. The saponins may also be formulated with excipients such as Carbopol<sup>R</sup> to increase viscosity, or may be formulated in a dry powder form with a powder excipient such as lactose.

In one preferred embodiment, the adjuvant system includes the

25 combination of a monophosphoryl lipid A and a saponin derivative, such as the combination of QS21 and 3D-MPL<sup>®</sup> adjuvant, as described in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol, as described in WO 96/33739. Other preferred formulations comprise an oil-in-water emulsion and tocopherol. Another particularly preferred adjuvant formulation employing QS21, 3D-

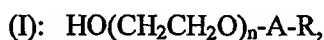


MPL<sup>®</sup> adjuvant and tocopherol in an oil-in-water emulsion is described in WO 95/17210.

Another enhanced adjuvant system involves the combination of a CpG-containing oligonucleotide and a saponin derivative particularly the combination of  
5 CpG and QS21 is disclosed in WO 00/09159. Preferably the formulation additionally comprises an oil in water emulsion and tocopherol.

Additional illustrative adjuvants for use in the pharmaceutical compositions of the invention include Montanide ISA 720 (Seppic, France), SAF (Chiron, California, United States), ISCOMS (CSL), MF-59 (Chiron), the SBAS series  
10 of adjuvants (e.g., SBAS-2 or SBAS-4, available from SmithKline Beecham, Rixensart, Belgium), Detox (Enhanzyn<sup>®</sup>; Corixa, Hamilton, MT), RC-529 (Corixa, Hamilton, MT) and other aminoalkyl glucosaminide 4-phosphates (AGPs), such as those described in pending U.S. Patent Application Serial Nos. 08/853,826 and 09/074,720, the disclosures of which are incorporated herein by reference in their entireties, and polyoxyethylene  
15 ether adjuvants such as those described in WO 99/52549A1.

Other preferred adjuvants include adjuvant molecules of the general formula



wherein,  $n$  is 1-50,  $A$  is a bond or  $-\text{C}(\text{O})-$ ,  $R$  is  $\text{C}_{1-50}$  alkyl or Phenyl  $\text{C}_{1-50}$  alkyl.

20 One embodiment of the present invention consists of a vaccine formulation comprising a polyoxyethylene ether of general formula (I), wherein  $n$  is between 1 and 50, preferably 4-24, most preferably 9; the  $R$  component is  $\text{C}_{1-50}$ , preferably  $\text{C}_4\text{-C}_{20}$  alkyl and most preferably  $\text{C}_{12}$  alkyl, and  $A$  is a bond. The concentration of the polyoxyethylene ethers should be in the range 0.1-20%, preferably  
25 from 0.1-10%, and most preferably in the range 0.1-1%. Preferred polyoxyethylene ethers are selected from the following group: polyoxyethylene-9-lauryl ether, polyoxyethylene-9-stearyl ether, polyoxyethylene-8-stearyl ether, polyoxyethylene-4-lauryl ether, polyoxyethylene-35-lauryl ether, and polyoxyethylene-23-lauryl ether. Polyoxyethylene ethers such as polyoxyethylene lauryl ether are described in the Merck  
30 index (12<sup>th</sup> edition: entry 7717). These adjuvant molecules are described in WO

99/52549. The polyoxyethylene ether according to the general formula (I) above may, if desired, be combined with another adjuvant. For example, a preferred adjuvant combination is preferably with CpG as described in the pending UK patent application GB 9820956.2.

5                   According to another embodiment of this invention, an immunogenic composition described herein is delivered to a host via antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified to increase the capacity for presenting the antigen, to improve activation and/or  
10 maintenance of the T cell response, to have anti-tumor effects *per se* and/or to be immunologically compatible with the receiver (*i.e.*, matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs, including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic or xenogeneic cells.

15                   Certain preferred embodiments of the present invention use dendritic cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature* 392:245-251, 1998) and have been shown to be effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (*see* Timmerman and Levy, *Ann. Rev. Med.* 50:507-529, 1999). In  
20 general, dendritic cells may be identified based on their typical shape (stellate *in situ*, with marked cytoplasmic processes (dendrites) visible *in vitro*), their ability to take up, process and present antigens with high efficiency and their ability to activate naïve T cell responses. Dendritic cells may, of course, be engineered to express specific cell-surface receptors or ligands that are not commonly found on dendritic cells *in vivo* or *ex*  
25 *vivo*, and such modified dendritic cells are contemplated by the present invention. As an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within a vaccine (*see* Zitvogel et al., *Nature Med.* 4:594-600, 1998).

                  Dendritic cells and progenitors may be obtained from peripheral blood,  
30 bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph

nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of cytokines such as GM-CSF, IL-4, IL-13 and/or TNF $\alpha$  to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from  
5 peripheral blood, umbilical cord blood or bone marrow may be differentiated into dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNF $\alpha$ , CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce differentiation, maturation and proliferation of dendritic cells.

Dendritic cells are conveniently categorized as "immature" and "mature"  
10 cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC with a high capacity for antigen uptake and processing, which correlates with the high expression of Fc $\gamma$  receptor and mannose receptor. The mature  
15 phenotype is typically characterized by a lower expression of these markers, but a high expression of cell surface molecules responsible for T cell activation such as class I and class II MHC, adhesion molecules (*e.g.*, CD54 and CD11) and costimulatory molecules (*e.g.*, CD40, CD80, CD86 and 4-1BB).

APCs may generally be transfected with a polynucleotide of the  
20 invention (or portion or other variant thereof) such that the encoded polypeptide, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place *ex vivo*, and a pharmaceutical composition comprising such transfected cells may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be  
25 administered to a patient, resulting in transfection that occurs *in vivo*. *In vivo* and *ex vivo* transfection of dendritic cells, for example, may generally be performed using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach described by Mahvi et al., *Immunology and cell Biology* 75:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or  
30 progenitor cells with the tumor polypeptide, DNA (naked or within a plasmid vector) or

RNA; or with antigen-expressing recombinant bacterium or viruses (*e.g.*, vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently conjugated to an immunological partner that provides T cell help (*e.g.*, a carrier molecule). Alternatively, a dendritic cell may be pulsed with a non-conjugated  
5 immunological partner, separately or in the presence of the polypeptide.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will typically vary depending on the mode of administration. Compositions of the present invention may be formulated for any appropriate manner of administration,  
10 including for example, topical, oral, nasal, mucosal, intravenous, intracranial, intraperitoneal, subcutaneous and intramuscular administration.

Carriers for use within such pharmaceutical compositions are biocompatible, and may also be biodegradable. In certain embodiments, the formulation preferably provides a relatively constant level of active component release.  
15 In other embodiments, however, a more rapid rate of release immediately upon administration may be desired. The formulation of such compositions is well within the level of ordinary skill in the art using known techniques. Illustrative carriers useful in this regard include microparticles of poly(lactide-co-glycolide), polyacrylate, latex, starch, cellulose, dextran and the like. Other illustrative delayed-release carriers  
20 include supramolecular biovectors, which comprise a non-liquid hydrophilic core (*e.g.*, a cross-linked polysaccharide or oligosaccharide) and, optionally, an external layer comprising an amphiphilic compound, such as a phospholipid (*see e.g.*, U.S. Patent No. 5,151,254 and PCT applications WO 94/20078, WO/94/23701 and WO 96/06638). The amount of active compound contained within a sustained release formulation depends  
25 upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

In another illustrative embodiment, biodegradable microspheres (*e.g.*, polylactate polyglycolate) are employed as carriers for the compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S.  
30 Patent Nos. 4,897,268; 5,075,109; 5,928,647; 5,811,128; 5,820,883; 5,853,763;

5,814,344, 5,407,609 and 5,942,252. Modified hepatitis B core protein carrier systems, such as described in WO/99 40934, and references cited therein, will also be useful for many applications. Another illustrative carrier/delivery system employs a carrier comprising particulate-protein complexes, such as those described in U.S. Patent No. 5,928,647, which are capable of inducing a class I-restricted cytotoxic T lymphocyte responses in a host.

The pharmaceutical compositions of the invention will often further comprise one or more buffers (*e.g.*, neutral buffered saline or phosphate buffered saline), carbohydrates (*e.g.*, glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, bacteriostats, chelating agents such as EDTA or glutathione, adjuvants (*e.g.*, aluminum hydroxide), solutes that render the formulation isotonic, hypotonic or weakly hypertonic with the blood of a recipient, suspending agents, thickening agents and/or preservatives. Alternatively, compositions of the present invention may be formulated as a lyophilizate.

The pharmaceutical compositions described herein may be presented in unit-dose or multi-dose containers, such as sealed ampoules or vials. Such containers are typically sealed in such a way to preserve the sterility and stability of the formulation until use. In general, formulations may be stored as suspensions, solutions or emulsions in oily or aqueous vehicles. Alternatively, a pharmaceutical composition may be stored in a freeze-dried condition requiring only the addition of a sterile liquid carrier immediately prior to use.

The development of suitable dosing and treatment regimens for using the particular compositions described herein in a variety of treatment regimens, including *e.g.*, oral, parenteral, intravenous, intranasal, and intramuscular administration and formulation, is well known in the art, some of which are briefly discussed below for general purposes of illustration.

In certain applications, the pharmaceutical compositions disclosed herein may be delivered *via* oral administration to an animal. As such, these compositions may be formulated with an inert diluent or with an assimilable edible carrier, or they

may be enclosed in hard- or soft-shell gelatin capsule, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet.

The active compounds may even be incorporated with excipients and used in the form of ingestible tablets, buccal tables, troches, capsules, elixirs, suspensions, syrups, wafers, and the like (see, for example, Mathiowitz *et al.*, Nature 1997 Mar 27;386(6623):410-4; Hwang *et al.*, Crit Rev Ther Drug Carrier Syst 1998;15(3):243-84; U. S. Patent 5,641,515; U. S. Patent 5,580,579 and U. S. Patent 5,792,451). Tablets, troches, pills, capsules and the like may also contain any of a variety of additional components, for example, a binder, such as gum tragacanth, acacia, cornstarch, or gelatin; excipients, such as dicalcium phosphate; a disintegrating agent, such as corn starch, potato starch, alginic acid and the like; a lubricant, such as magnesium stearate; and a sweetening agent, such as sucrose, lactose or saccharin may be added or a flavoring agent, such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar, or both. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compounds may be incorporated into sustained-release preparation and formulations.

Typically, these formulations will contain at least about 0.1% of the active compound or more, although the percentage of the active ingredient(s) may, of course, be varied and may conveniently be between about 1 or 2% and about 60% or 70% or more of the weight or volume of the total formulation. Naturally, the amount of active compound(s) in each therapeutically useful composition may be prepared in such a way that a suitable dosage will be obtained in any given unit dose of the compound. Factors such as solubility, bioavailability, biological half-life, route of administration, product shelf life, as well as other pharmacological considerations will be contemplated by one skilled in the art of preparing such pharmaceutical formulations, and as such, a variety of dosages and treatment regimens may be desirable.

For oral administration, the compositions of the present invention may alternatively be incorporated with one or more excipients in the form of a mouthwash, dentifrice, buccal tablet, oral spray, or sublingual orally-administered formulation. Alternatively, the active ingredient may be incorporated into an oral solution such as  
5 one containing sodium borate, glycerin and potassium bicarbonate, or dispersed in a dentifrice, or added in a therapeutically-effective amount to a composition that may include water, binders, abrasives, flavoring agents, foaming agents, and humectants. Alternatively the compositions may be fashioned into a tablet or solution form that may be placed under the tongue or otherwise dissolved in the mouth.

10 In certain circumstances it will be desirable to deliver the pharmaceutical compositions disclosed herein parenterally, intravenously, intramuscularly, or even intraperitoneally. Such approaches are well known to the skilled artisan, some of which are further described, for example, in U. S. Patent 5,543,158; U. S. Patent 5,641,515 and U. S. Patent 5,399,363. In certain embodiments, solutions of the active compounds  
15 as free base or pharmacologically acceptable salts may be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions may also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations generally will contain a preservative to prevent the growth of microorganisms.

20 Illustrative pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions (for example, see U. S. Patent 5,466,468). In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and  
25 storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and/or vegetable oils. Proper fluidity may be maintained, for example, by the use of a coating, such as  
30 lecithin, by the maintenance of the required particle size in the case of dispersion and/or

by the use of surfactants. The prevention of the action of microorganisms can be facilitated by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride.

5 Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

In one embodiment, for parenteral administration in an aqueous solution, the solution should be suitably buffered if necessary and the liquid diluent first rendered

10 isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, a sterile aqueous medium that can be employed will be known to those of skill in the art in light of the present disclosure. For example, one dosage may be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml

15 of hypodermoclysis fluid or injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences" 15th Edition, pages 1035-1038 and 1570-1580). Some variation in dosage will necessarily occur depending on the condition of the subject being treated. Moreover, for human administration, preparations will of course preferably meet sterility, pyrogenicity, and the general safety and purity

20 standards as required by FDA Office of Biologics standards.

In another embodiment of the invention, the compositions disclosed herein may be formulated in a neutral or salt form. Illustrative pharmaceutically-acceptable salts include the acid addition salts (formed with the free amino groups of the protein) and which are formed with inorganic acids such as, for

25 example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like. Upon formulation, solutions will be



administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective.

The carriers can further comprise any and all solvents, dispersion media, vehicles, coatings, diluents, antibacterial and antifungal agents, isotonic and absorption  
5 delaying agents, buffers, carrier solutions, suspensions, colloids, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions. The phrase  
10 "pharmaceutically-acceptable" refers to molecular entities and compositions that do not produce an allergic or similar untoward reaction when administered to a human.

In certain embodiments, the pharmaceutical compositions may be delivered by intranasal sprays, inhalation, and/or other aerosol delivery vehicles. Methods for delivering genes, nucleic acids, and peptide compositions directly to the  
15 lungs *via* nasal aerosol sprays has been described, *e.g.*, in U. S. Patent 5,756,353 and U. S. Patent 5,804,212. Likewise, the delivery of drugs using intranasal microparticle resins (Takenaga *et al.*, J Controlled Release 1998 Mar 2;52(1-2):81-7) and lysophosphatidyl-glycerol compounds (U. S. Patent 5,725,871) are also well-known in the pharmaceutical arts. Likewise, illustrative transmucosal drug delivery in the form of  
20 a polytetrafluoroethylene support matrix is described in U. S. Patent 5,780,045.

In certain embodiments, liposomes, nanocapsules, microparticles, lipid particles, vesicles, and the like, are used for the introduction of the compositions of the present invention into suitable host cells/organisms. In particular, the compositions of the present invention may be formulated for delivery either encapsulated in a lipid  
25 particle, a liposome, a vesicle, a nanosphere, or a nanoparticle or the like. Alternatively, compositions of the present invention can be bound, either covalently or non-covalently, to the surface of such carrier vehicles.

The formation and use of liposome and liposome-like preparations as potential drug carriers is generally known to those of skill in the art (see for example,  
30 Lasic, Trends Biotechnol 1998 Jul;16(7):307-21; Takakura, Nippon Rinsho 1998

Mar;56(3):691-5; Chandran *et al.*, Indian J Exp Biol. 1997 Aug;35(8):801-9; Margalit, Crit Rev Ther Drug Carrier Syst. 1995;12(2-3):233-61; U.S. Patent 5,567,434; U.S. Patent 5,552,157; U.S. Patent 5,565,213; U.S. Patent 5,738,868 and U.S. Patent 5,795,587, each specifically incorporated herein by reference in its entirety).

5               Liposomes have been used successfully with a number of cell types that are normally difficult to transfect by other procedures, including T cell suspensions, primary hepatocyte cultures and PC 12 cells (Renneisen *et al.*, J Biol Chem. 1990 Sep 25;265(27):16337-42; Muller *et al.*, DNA Cell Biol. 1990 Apr;9(3):221-9). In addition, liposomes are free of the DNA length constraints that are typical of viral-based delivery  
10 systems. Liposomes have been used effectively to introduce genes, various drugs, radiotherapeutic agents, enzymes, viruses, transcription factors, allosteric effectors and the like, into a variety of cultured cell lines and animals. Furthermore, the use of liposomes does not appear to be associated with autoimmune responses or unacceptable toxicity after systemic delivery.

15               In certain embodiments, liposomes are formed from phospholipids that are dispersed in an aqueous medium and spontaneously form multilamellar concentric bilayer vesicles (also termed multilamellar vesicles (MLVs)).

                  Alternatively, in other embodiments, the invention provides for pharmaceutically-acceptable nanocapsule formulations of the compositions of the  
20 present invention. Nanocapsules can generally entrap compounds in a stable and reproducible way (see, for example, Quintanar-Guerrero *et al.*, Drug Dev Ind Pharm. 1998 Dec;24(12):1113-28). To avoid side effects due to intracellular polymeric overloading, such ultrafine particles (sized around 0.1  $\mu\text{m}$ ) may be designed using polymers able to be degraded *in vivo*. Such particles can be made as described, for  
25 example, by Couvreur *et al.*, Crit Rev Ther Drug Carrier Syst. 1988;5(1):1-20; zur Muhlen *et al.*, Eur J Pharm Biopharm. 1998 Mar;45(2):149-55; Zambaux *et al.* J Controlled Release. 1998 Jan 2;50(1-3):31-40; and U. S. Patent 5,145,684.

Cancer Therapeutic Methods

In further aspects of the present invention, the pharmaceutical compositions described herein may be used for the treatment of cancer, particularly for the immunotherapy of prostate cancer. Within such methods, the pharmaceutical compositions described herein are administered to a patient, typically a warm-blooded animal, preferably a human. A patient may or may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions may be used to prevent the development of a cancer or to treat a patient afflicted with a cancer. Pharmaceutical compositions and vaccines may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration of radiotherapy or conventional chemotherapeutic drugs. As discussed above, administration of the pharmaceutical compositions may be by any suitable method, including administration by intravenous, intraperitoneal, intramuscular, subcutaneous, intranasal, intradermal, anal, vaginal, topical and oral routes.

Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immune response-modifying agents (such as polypeptides and polynucleotides as provided herein).

Within other embodiments, immunotherapy may be passive immunotherapy, in which treatment involves the delivery of agents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T cells as discussed above, T lymphocytes (such as CD8<sup>+</sup> cytotoxic T lymphocytes and CD4<sup>+</sup> T-helper tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokine-activated killer cells), B cells and antigen-presenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other vectors or effector cells for adoptive immunotherapy. The

polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth *in vitro*, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition *in vivo* are well known in the art. Such *in vitro* culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast and/or B cells, may be pulsed with immunoreactive polypeptides or transfected with one or more polynucleotides using standard techniques well known in the art. For example, antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system. Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term *in vivo*. Studies have shown that cultured effector cells can be induced to grow *in vivo* and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (see, for example, Cheever et al., *Immunological Reviews* 157:177, 1997).

Alternatively, a vector expressing a polypeptide recited herein may be introduced into antigen presenting cells taken from a patient and clonally propagated *ex vivo* for transplant back into the same patient. Transfected cells may be reintroduced into the patient using any means known in the art, preferably in sterile form by intravenous, intracavitary, intraperitoneal or intratumor administration.

Routes and frequency of administration of the therapeutic compositions described herein, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and vaccines may be administered by injection (e.g., intracutaneous,

intramuscular, intravenous or subcutaneous), intranasally (*e.g.*, by aspiration) or orally. Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50% above the basal (*i.e.*, untreated) level. Such response can be monitored by measuring the anti-tumor antibodies in a patient or by vaccine-dependent generation of cytolytic effector cells capable of killing the patient's tumor cells *in vitro*. Such vaccines should also be capable of causing an immune response that leads to an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial or longer disease-free survival) in vaccinated patients as compared to non-vaccinated patients. In general, for pharmaceutical compositions and vaccines comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 25 µg to 5 mg per kg of host. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. Increases in preexisting immune responses to a tumor protein generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

#### Cancer Detection and Diagnostic Compositions, Methods and Kits

In general, a cancer may be detected in a patient based on the presence of one or more prostate tumor proteins and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, sputum urine and/or tumor biopsies)

obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as prostate cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the  
5 biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, a prostate tumor sequence should be present at a level that is at least three fold higher in tumor tissue than in normal tissue

There are a variety of assay formats known to those of ordinary skill in  
10 the art for using a binding agent to detect polypeptide markers in a sample. *See, e.g.,* Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c)  
15 comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding  
20 agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized  
25 binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include full length prostate tumor proteins and polypeptide portions thereof to which the binding agent binds, as  
30 described above.

The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10  $\mu$ g, and preferably about 100 ng to about 1  $\mu$ g, is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (*see, e.g.,* Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized

on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20™ (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with prostate cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20™. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

The detection reagent is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound detection reagent is then removed



and bound detection reagent is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

10 To determine the presence or absence of a cancer, such as prostate cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with  
15 samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., *Clinical Epidemiology: A Basic Science for Clinical Medicine*, Little Brown and Co., 1985,  
20 p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (*i.e.*, sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (*i.e.*, the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a  
25 signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second binding agent and to the area of immobilized binding agent. Concentration of second binding agent at the area of immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of binding agent immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1  $\mu$ g, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use tumor polypeptides to detect antibodies that bind to such polypeptides in a biological sample. The detection of such tumor protein specific antibodies may correlate with the presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with a tumor protein in a biological sample. Within certain methods, a biological sample comprising CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells isolated from a patient is incubated with a tumor polypeptide, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated *in vitro* for 2-9 days (typically 4 days) at 37°C with polypeptide (e.g., 5 - 25 µg/ml). It may be desirable to incubate another aliquot of a T cell sample in the absence of tumor polypeptide to serve as a control. For CD4<sup>+</sup> T cells, activation is preferably detected by evaluating proliferation of the T cells. For CD8<sup>+</sup> T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding a tumor protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify a portion of a tumor cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*, hybridizes to) a polynucleotide encoding the tumor protein. The amplified cDNA is then separated and detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding a tumor protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding a tumor protein of the invention that is at least 10

nucleotides, and preferably at least 20 nucleotides, in length. Preferably, oligonucleotide primers and/or probes hybridize to a polynucleotide encoding a polypeptide described herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the  
5 diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers comprise at least 10 contiguous nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence as disclosed herein. Techniques for both PCR based assays and hybridization assays are well known in the art (*see, for example, Mullis et al., Cold*  
10 *Spring Harbor Symp. Quant. Biol.*, 51:263, 1987; Erlich ed., *PCR Technology*, Stockton Press, NY, 1989).

One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample, such as biopsy tissue, and is reverse transcribed to produce cDNA molecules.  
15 PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken from a test patient and from an individual who is not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold  
20 or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

In another embodiment, the compositions described herein may be used as markers for the progression of cancer. In this embodiment, assays as described above  
25 for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) or polynucleotide(s) evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide or polynucleotide detected increases over time. In contrast, the

cancer is not progressing when the level of reactive polypeptide or polynucleotide either remains constant or decreases with time.

Certain *in vivo* diagnostic assays may be performed directly on a tumor. One such assay involves contacting tumor cells with a binding agent. The bound  
5 binding agent may then be detected directly or indirectly via a reporter group. Such binding agents may also be used in histological applications. Alternatively, polynucleotide probes may be used within such applications.

As noted above, to improve sensitivity, multiple tumor protein markers may be assayed within a given sample. It will be apparent that binding agents specific  
10 for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor protein markers may be based on routine experiments to determine combinations that results in optimal sensitivity. In addition, or alternatively, assays for tumor proteins provided herein may be combined with assays for other known tumor antigens.

15 The present invention further provides kits for use within any of the above diagnostic methods. Such kits typically comprise two or more components necessary for performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a monoclonal antibody or fragment thereof that specifically binds to a tumor protein.  
20 Such antibodies or fragments may be provided attached to a support material, as described above. One or more additional containers may enclose elements, such as reagents or buffers, to be used in the assay. Such kits may also, or alternatively, contain a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

25 Alternatively, a kit may be designed to detect the level of mRNA encoding a tumor protein in a biological sample. Such kits generally comprise at least one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding a tumor protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that may be

present within such kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate the detection of a polynucleotide encoding a tumor protein.

The following Examples are offered by way of illustration and not by way of limitation.

5

## EXAMPLES

### EXAMPLE 1

#### ISOLATION AND CHARACTERIZATION OF PROSTATE-SPECIFIC POLYPEPTIDES

10

This Example describes the isolation of certain prostate-specific polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library was constructed from prostate tumor poly A<sup>+</sup> RNA using a Superscript Plasmid System for cDNA Synthesis and Plasmid Cloning kit (BRL Life Technologies, Gaithersburg, MD 20897) following  
15 the manufacturer's protocol. Specifically, prostate tumor tissues were homogenized with polytron (Kinematica, Switzerland) and total RNA was extracted using Trizol reagent (BRL Life Technologies) as directed by the manufacturer. The poly A<sup>+</sup> RNA was then purified using a Qiagen oligotex spin column mRNA purification kit (Qiagen,  
20 Santa Clarita, CA 91355) according to the manufacturer's protocol. First-strand cDNA was synthesized using the NotI/Oligo-dT18 primer. Double-stranded cDNA was synthesized, ligated with EcoRI/BAXI adaptors (Invitrogen, San Diego, CA) and digested with NotI. Following size fractionation with Chroma Spin-1000 columns (Clontech, Palo Alto, CA), the cDNA was ligated into the EcoRI/NotI site of  
25 pCDNA3.1 (Invitrogen) and transformed into ElectroMax *E. coli* DH10B cells (BRL Life Technologies) by electroporation.

Using the same procedure, a normal human pancreas cDNA expression library was prepared from a pool of six tissue specimens (Clontech). The cDNA libraries were characterized by determining the number of independent colonies, the  
30 percentage of clones that carried insert, the average insert size and by sequence analysis.

The prostate tumor library contained  $1.64 \times 10^7$  independent colonies, with 70% of clones having an insert and the average insert size being 1745 base pairs. The normal pancreas cDNA library contained  $3.3 \times 10^6$  independent colonies, with 69% of clones having inserts and the average insert size being 1120 base pairs. For both libraries, sequence analysis showed that the majority of clones had a full length cDNA sequence and were synthesized from mRNA, with minimal rRNA and mitochondrial DNA contamination.

cDNA library subtraction was performed using the above prostate tumor and normal pancreas cDNA libraries, as described by Hara *et al.* (*Blood*, 84:189-199, 1994) with some modifications. Specifically, a prostate tumor-specific subtracted cDNA library was generated as follows. Normal pancreas cDNA library (70  $\mu$ g) was digested with EcoRI, NotI, and SfuI, followed by a filling-in reaction with DNA polymerase Klenow fragment. After phenol-chloroform extraction and ethanol precipitation, the DNA was dissolved in 100  $\mu$ l of H<sub>2</sub>O, heat-denatured and mixed with 100  $\mu$ l (100  $\mu$ g) of Photoprobe biotin (Vector Laboratories, Burlingame, CA). As recommended by the manufacturer, the resulting mixture was irradiated with a 270 W sunlamp on ice for 20 minutes. Additional Photoprobe biotin (50  $\mu$ l) was added and the biotinylation reaction was repeated. After extraction with butanol five times, the DNA was ethanol-precipitated and dissolved in 23  $\mu$ l H<sub>2</sub>O to form the driver DNA.

To form the tracer DNA, 10  $\mu$ g prostate tumor cDNA library was digested with BamHI and XhoI, phenol chloroform extracted and passed through Chroma spin-400 columns (Clontech). Following ethanol precipitation, the tracer DNA was dissolved in 5  $\mu$ l H<sub>2</sub>O. Tracer DNA was mixed with 15  $\mu$ l driver DNA and 20  $\mu$ l of 2 x hybridization buffer (1.5 M NaCl/10 mM EDTA/50 mM HEPES pH 7.5/0.2% sodium dodecyl sulfate), overlaid with mineral oil, and heat-denatured completely. The sample was immediately transferred into a 68 °C water bath and incubated for 20 hours (long hybridization [LH]). The reaction mixture was then subjected to a streptavidin treatment followed by phenol/chloroform extraction. This process was repeated three more times. Subtracted DNA was precipitated, dissolved in 12  $\mu$ l H<sub>2</sub>O, mixed with 8  $\mu$ l driver DNA and 20  $\mu$ l of 2 x hybridization buffer, and subjected to a hybridization at 68

<sup>0</sup>C for 2 hours (short hybridization [SH]). After removal of biotinylated double-stranded DNA, subtracted cDNA was ligated into BamHI/XhoI site of chloramphenicol resistant pBCSK<sup>+</sup> (Stratagene, La Jolla, CA 92037) and transformed into ElectroMax *E. coli* DH10B cells by electroporation to generate a prostate tumor specific subtracted  
5 cDNA library (referred to as "prostate subtraction 1").

To analyze the subtracted cDNA library, plasmid DNA was prepared from 100 independent clones, randomly picked from the subtracted prostate tumor specific library and grouped based on insert size. Representative cDNA clones were further characterized by DNA sequencing with a Perkin Elmer/Applied Biosystems  
10 Division Automated Sequencer Model 373A (Foster City, CA). Six cDNA clones, hereinafter referred to as F1-13, F1-12, F1-16, H1-1, H1-9 and H1-4, were shown to be abundant in the subtracted prostate-specific cDNA library. The determined 3' and 5' cDNA sequences for F1-12 are provided in SEQ ID NO: 2 and 3, respectively, with determined 3' cDNA sequences for F1-13, F1-16, H1-1, H1-9 and H1-4 being provided  
15 in SEQ ID NO: 1 and 4-7, respectively.

The cDNA sequences for the isolated clones were compared to known sequences in the gene bank using the EMBL and GenBank databases (release 96). Four of the prostate tumor cDNA clones, F1-13, F1-16, H1-1, and H1-4, were determined to encode the following previously identified proteins: prostate specific antigen (PSA),  
20 human glandular kallikrein, human tumor expression enhanced gene, and mitochondria cytochrome C oxidase subunit II. H1-9 was found to be identical to a previously identified human autonomously replicating sequence. No significant homologies to the cDNA sequence for F1-12 were found.

Subsequent studies led to the isolation of a full-length cDNA sequence  
25 for F1-12 (also referred to as P504S). This sequence is provided in SEQ ID NO: 107, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 108. cDNA splice variants of P504S are provided in SEQ ID NO: 600-605.

To clone less abundant prostate tumor specific genes, cDNA library subtraction was performed by subtracting the prostate tumor cDNA library described  
30 above with the normal pancreas cDNA library and with the three most abundant genes



in the previously subtracted prostate tumor specific cDNA library: human glandular kallikrein, prostate specific antigen (PSA), and mitochondria cytochrome C oxidase subunit II. Specifically, 1  $\mu$ g each of human glandular kallikrein, PSA and mitochondria cytochrome C oxidase subunit II cDNAs in pCDNA3.1 were added to the driver DNA and subtraction was performed as described above to provide a second subtracted cDNA library hereinafter referred to as the "subtracted prostate tumor specific cDNA library with spike".

Twenty-two cDNA clones were isolated from the subtracted prostate tumor specific cDNA library with spike. The determined 3' and 5' cDNA sequences for the clones referred to as J1-17, L1-12, N1-1862, J1-13, J1-19, J1-25, J1-24, K1-58, K1-63, L1-4 and L1-14 are provided in SEQ ID NOS: 8-9, 10-11, 12-13, 14-15, 16-17, 18-19, 20-21, 22-23, 24-25, 26-27 and 28-29, respectively. The determined 3' cDNA sequences for the clones referred to as J1-12, J1-16, J1-21, K1-48, K1-55, L1-2, L1-6, N1-1858, N1-1860, N1-1861, N1-1864 are provided in SEQ ID NOS: 30-40, respectively. Comparison of these sequences with those in the gene bank as described above, revealed no significant homologies to three of the five most abundant DNA species, (J1-17, L1-12 and N1-1862; SEQ ID NOS: 8-9, 10-11 and 12-13, respectively). Of the remaining two most abundant species, one (J1-12; SEQ ID NO:30) was found to be identical to the previously identified human pulmonary surfactant-associated protein, and the other (K1-48; SEQ ID NO:33) was determined to have some homology to *R. norvegicus* mRNA for 2-arylpropionyl-CoA epimerase. Of the 17 less abundant cDNA clones isolated from the subtracted prostate tumor specific cDNA library with spike, four (J1-16, K1-55, L1-6 and N1-1864; SEQ ID NOS:31, 34, 36 and 40, respectively) were found to be identical to previously identified sequences, two (J1-21 and N1-1860; SEQ ID NOS: 32 and 38, respectively) were found to show some homology to non-human sequences, and two (L1-2 and N1-1861; SEQ ID NOS: 35 and 39, respectively) were found to show some homology to known human sequences. No significant homologies were found to the polypeptides J1-13, J1-19, J1-24, J1-25, K1-58, K1-63, L1-4, L1-14 (SEQ ID NOS: 14-15, 16-17, 20-21, 18-19, 22-23, 24-25, 26-27, 28-29, respectively).

Subsequent studies led to the isolation of full length cDNA sequences for J1-17, L1-12 and N1-1862 (SEQ ID NOS: 109-111, respectively). The corresponding predicted amino acid sequences are provided in SEQ ID NOS: 112-114. L1-12 is also referred to as P501S. A cDNA splice variant of P501S is provided in SEQ ID NO: 606.

5 In a further experiment, four additional clones were identified by subtracting a prostate tumor cDNA library with normal prostate cDNA prepared from a pool of three normal prostate poly A+ RNA (referred to as "prostate subtraction 2"). The determined cDNA sequences for these clones, hereinafter referred to as U1-3064, U1-3065, V1-3692 and 1A-3905, are provided in SEQ ID NO: 69-72, respectively.

10 Comparison of the determined sequences with those in the gene bank revealed no significant homologies to U1-3065.

A second subtraction with spike (referred to as "prostate subtraction spike 2") was performed by subtracting a prostate tumor specific cDNA library with spike with normal pancreas cDNA library and further spiked with PSA, J1-17,

15 pulmonary surfactant-associated protein, mitochondrial DNA, cytochrome c oxidase subunit II, N1-1862, autonomously replicating sequence, L1-12 and tumor expression enhanced gene. Four additional clones, hereinafter referred to as V1-3686, R1-2330, 1B-3976 and V1-3679, were isolated. The determined cDNA sequences for these clones are provided in SEQ ID NO: 73-76, respectively. Comparison of these sequences

20 with those in the gene bank revealed no significant homologies to V1-3686 and R1-2330.

Further analysis of the three prostate subtractions described above (prostate subtraction 2, subtracted prostate tumor specific cDNA library with spike, and prostate subtraction spike 2) resulted in the identification of sixteen additional clones,

25 referred to as 1G-4736, 1G-4738, 1G-4741, 1G-4744, 1G-4734, 1H-4774, 1H-4781, 1H-4785, 1H-4787, 1H-4796, 1I-4810, 1I-4811, 1J-4876, 1K-4884 and 1K-4896. The determined cDNA sequences for these clones are provided in SEQ ID NOS: 77-92, respectively. Comparison of these sequences with those in the gene bank as described above, revealed no significant homologies to 1G-4741, 1G-4734, 1I-4807, 1J-4876 and

30 1K-4896 (SEQ ID NOS: 79, 81, 87, 90 and 92, respectively). Further analysis of the

isolated clones led to the determination of extended cDNA sequences for 1G-4736, 1G-4738, 1G-4741, 1G-4744, 1H-4774, 1H-4781, 1H-4785, 1H-4787, 1H-4796, 1I-4807, 1J-4876, 1K-4884 and 1K-4896, provided in SEQ ID NOS: 179-188 and 191-193, respectively, and to the determination of additional partial cDNA sequences for 1I-4810  
5 and 1I-4811, provided in SEQ ID NOS: 189 and 190, respectively.

Additional studies with prostate subtraction spike 2 resulted in the isolation of three more clones. Their sequences were determined as described above and compared to the most recent GenBank. All three clones were found to have homology to known genes, which are Cysteine-rich protein, KIAA0242, and KIAA0280  
10 (SEQ ID NO: 317, 319, and 320, respectively). Further analysis of these clones by Synteni microarray (Synteni, Palo Alto, CA) demonstrated that all three clones were over-expressed in most prostate tumors and prostate BPH, as well as in the majority of normal prostate tissues tested, but low expression in all other normal tissues.

An additional subtraction was performed by subtracting a normal  
15 prostate cDNA library with normal pancreas cDNA (referred to as "prostate subtraction 3"). This led to the identification of six additional clones referred to as 1G-4761, 1G-4762, 1H-4766, 1H-4770, 1H-4771 and 1H-4772 (SEQ ID NOS: 93-98). Comparison of these sequences with those in the gene bank revealed no significant homologies to 1G-4761 and 1H-4771 (SEQ ID NOS: 93 and 97, respectively). Further analysis of the  
20 isolated clones led to the determination of extended cDNA sequences for 1G-4761, 1G-4762, 1H-4766 and 1H-4772 provided in SEQ ID NOS: 194-196 and 199, respectively, and to the determination of additional partial cDNA sequences for 1H-4770 and 1H-4771, provided in SEQ ID NOS: 197 and 198, respectively.

Subtraction of a prostate tumor cDNA library, prepared from a pool of  
25 polyA+ RNA from three prostate cancer patients, with a normal pancreas cDNA library (prostate subtraction 4) led to the identification of eight clones, referred to as 1D-4297, 1D-4309, 1D-4278, 1D-4288, 1D-4283, 1D-4304, 1D-4296 and 1D-4280 (SEQ ID NOS: 99-107). These sequences were compared to those in the gene bank as described above. No significant homologies were found to 1D-4283 and 1D-4304 (SEQ ID NOS:  
30 103 and 104, respectively). Further analysis of the isolated clones led to the

determination of extended cDNA sequences for 1D-4309, 1D-4278, 1D-4288, 1D-4283, 1D-4304, 1D-4296 and 1D-4280, provided in SEQ ID NOS: 200-206, respectively.

cDNA clones isolated in prostate subtraction 1 and prostate subtraction  
5 2, described above, were colony PCR amplified and their mRNA expression levels in prostate tumor, normal prostate and in various other normal tissues were determined using microarray technology (Synteni, Palo Alto, CA). Briefly, the PCR amplification products were dotted onto slides in an array format, with each product occupying a unique location in the array. mRNA was extracted from the tissue sample to be tested,  
10 reverse transcribed, and fluorescent-labeled cDNA probes were generated. The microarrays were probed with the labeled cDNA probes, the slides scanned and fluorescence intensity was measured. This intensity correlates with the hybridization intensity. Two clones (referred to as P509S and P510S) were found to be over-expressed in prostate tumor and normal prostate and expressed at low levels in all other  
15 normal tissues tested (liver, pancreas, skin, bone marrow, brain, breast, adrenal gland, bladder, testes, salivary gland, large intestine, kidney, ovary, lung, spinal cord, skeletal muscle and colon). The determined cDNA sequences for P509S and P510S are provided in SEQ ID NO: 223 and 224, respectively. Comparison of these sequences with those in the gene bank as described above, revealed some homology to previously  
20 identified ESTs.

Additional studies led to the isolation of the full-length cDNA sequence for P509S. This sequence is provided in SEQ ID NO: 332, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 339. Two variant full-length cDNA sequences for P510S are provided in SEQ ID NO: 535 and 536, with the  
25 corresponding predicted amino acid sequences being provided in SEQ ID NO: 537 and 538, respectively. Additional splice variants of P510S are provided in SEQ ID NO: 598 and 599.

## EXAMPLE 2

## DETERMINATION OF TISSUE SPECIFICITY OF PROSTATE-SPECIFIC POLYPEPTIDES

Using gene specific primers, mRNA expression levels for the  
5 representative prostate-specific polypeptides F1-16, H1-1, J1-17 (also referred to as P502S), L1-12 (also referred to as P501S), F1-12 (also referred to as P504S) and N1-1862 (also referred to as P503S) were examined in a variety of normal and tumor tissues using RT-PCR.

Briefly, total RNA was extracted from a variety of normal and tumor  
10 tissues using Trizol reagent as described above. First strand synthesis was carried out using 1-2  $\mu$ g of total RNA with SuperScript II reverse transcriptase (BRL Life Technologies) at 42 °C for one hour. The cDNA was then amplified by PCR with gene-specific primers. To ensure the semi-quantitative nature of the RT-PCR,  $\beta$ -actin was used as an internal control for each of the tissues examined. First, serial dilutions of the  
15 first strand cDNAs were prepared and RT-PCR assays were performed using  $\beta$ -actin specific primers. A dilution was then chosen that enabled the linear range amplification of the  $\beta$ -actin template and which was sensitive enough to reflect the differences in the initial copy numbers. Using these conditions, the  $\beta$ -actin levels were determined for each reverse transcription reaction from each tissue. DNA contamination was  
20 minimized by DNase treatment and by assuring a negative PCR result when using first strand cDNA that was prepared without adding reverse transcriptase.

mRNA Expression levels were examined in four different types of tumor tissue (prostate tumor from 2 patients, breast tumor from 3 patients, colon tumor, lung tumor), and sixteen different normal tissues, including prostate, colon, kidney, liver,  
25 lung, ovary, pancreas, skeletal muscle, skin, stomach, testes, bone marrow and brain. F1-16 was found to be expressed at high levels in prostate tumor tissue, colon tumor and normal prostate, and at lower levels in normal liver, skin and testes, with expression being undetectable in the other tissues examined. H1-1 was found to be expressed at high levels in prostate tumor, lung tumor, breast tumor, normal prostate, normal colon  
30 and normal brain, at much lower levels in normal lung, pancreas, skeletal muscle, skin,

small intestine, bone marrow, and was not detected in the other tissues tested. J1-17 (P502S) and L1-12 (P501S) appear to be specifically over-expressed in prostate, with both genes being expressed at high levels in prostate tumor and normal prostate but at low to undetectable levels in all the other tissues examined. N1-1862 (P503S) was found to be over-expressed in 60% of prostate tumors and detectable in normal colon and kidney. The RT-PCR results thus indicate that F1-16, H1-1, J1-17 (P502S), N1-1862 (P503S) and L1-12 (P501S) are either prostate specific or are expressed at significantly elevated levels in prostate.

Further RT-PCR studies showed that F1-12 (P504S) is over-expressed in 60% of prostate tumors, detectable in normal kidney but not detectable in all other tissues tested. Similarly, R1-2330 was shown to be over-expressed in 40% of prostate tumors, detectable in normal kidney and liver, but not detectable in all other tissues tested. U1-3064 was found to be over-expressed in 60% of prostate tumors, and also expressed in breast and colon tumors, but was not detectable in normal tissues.

RT-PCR characterization of R1-2330, U1-3064 and 1D-4279 showed that these three antigens are over-expressed in prostate and/or prostate tumors.

Northern analysis with four prostate tumors, two normal prostate samples, two BPH prostates, and normal colon, kidney, liver, lung, pancreas, skeletal muscle, brain, stomach, testes, small intestine and bone marrow, showed that L1-12 (P501S) is over-expressed in prostate tumors and normal prostate, while being undetectable in other normal tissues tested. J1-17 (P502S) was detected in two prostate tumors and not in the other tissues tested. N1-1862 (P503S) was found to be over-expressed in three prostate tumors and to be expressed in normal prostate, colon and kidney, but not in other tissues tested. F1-12 (P504S) was found to be highly expressed in two prostate tumors and to be undetectable in all other tissues tested.

The microarray technology described above was used to determine the expression levels of representative antigens described herein in prostate tumor, breast tumor and the following normal tissues: prostate, liver, pancreas, skin, bone marrow, brain, breast, adrenal gland, bladder, testes, salivary gland, large intestine, kidney, ovary, lung, spinal cord, skeletal muscle and colon. L1-12 (P501S) was found to be

over-expressed in normal prostate and prostate tumor, with some expression being detected in normal skeletal muscle. Both J1-12 and F1-12 (P504S) were found to be over-expressed in prostate tumor, with expression being lower or undetectable in all other tissues tested. N1-1862 (P503S) was found to be expressed at high levels in prostate tumor and normal prostate, and at low levels in normal large intestine and normal colon, with expression being undetectable in all other tissues tested. R1-2330 was found to be over-expressed in prostate tumor and normal prostate, and to be expressed at lower levels in all other tissues tested. 1D-4279 was found to be over-expressed in prostate tumor and normal prostate, expressed at lower levels in normal spinal cord, and to be undetectable in all other tissues tested.

Further microarray analysis to specifically address the extent to which P501S (SEQ ID NO: 110) was expressed in breast tumor revealed moderate over-expression not only in breast tumor, but also in metastatic breast tumor (2/31), with negligible to low expression in normal tissues. This data suggests that P501S may be over-expressed in various breast tumors as well as in prostate tumors.

The expression levels of 32 ESTs (expressed sequence tags) described by Vasmatazis *et al.* (*Proc. Natl. Acad. Sci. USA* 95:300-304, 1998) in a variety of tumor and normal tissues were examined by microarray technology as described above. Two of these clones (referred to as P1000C and P1001C) were found to be over-expressed in prostate tumor and normal prostate, and expressed at low to undetectable levels in all other tissues tested (normal aorta, thymus, resting and activated PBMC, epithelial cells, spinal cord, adrenal gland, fetal tissues, skin, salivary gland, large intestine, bone marrow, liver, lung, dendritic cells, stomach, lymph nodes, brain, heart, small intestine, skeletal muscle, colon and kidney. The determined cDNA sequences for P1000C and P1001C are provided in SEQ ID NO: 384 and 472, respectively. The sequence of P1001C was found to show some homology to the previously isolated Human mRNA for JM27 protein. Subsequent comparison of the sequence of SEQ ID NO: 384 with sequences in the public databases, led to the identification of a full-length cDNA sequence of P1000C (SEQ ID NO: 786), which encodes a 492 amino acid sequence. Analysis of the amino acid sequence using the PSORT II program led to the

identification of a putative transmembrane domain from amino acids 84-100. The cDNA sequence of the open reading frame of P1000C, including the stop codon, is provided in SEQ ID NO: 787, with the open reading frame without the stop codon being provided in SEQ ID NO: 788. The full-length amino acid sequence of P1000C is  
5 provided in SEQ ID NO: 789. SEQ ID NO: 790 and 791 represent amino acids 1-100 and 100-492 of P1000C, respectively.

The expression of the polypeptide encoded by the full length cDNA sequence for F1-12 (also referred to as P504S; SEQ ID NO: 108) was investigated by immunohistochemical analysis. Rabbit-anti-P504S polyclonal antibodies were  
10 generated against the full length P504S protein by standard techniques. Subsequent isolation and characterization of the polyclonal antibodies were also performed by techniques well known in the art. Immunohistochemical analysis showed that the P504S polypeptide was expressed in 100% of prostate carcinoma samples tested (n=5).

The rabbit-anti-P504S polyclonal antibody did not appear to label benign  
15 prostate cells with the same cytoplasmic granular staining, but rather with light nuclear staining. Analysis of normal tissues revealed that the encoded polypeptide was found to be expressed in some, but not all normal human tissues. Positive cytoplasmic staining with rabbit-anti-P504S polyclonal antibody was found in normal human kidney, liver, brain, colon and lung-associated macrophages, whereas heart and bone marrow were  
20 negative.

This data indicates that the P504S polypeptide is present in prostate cancer tissues, and that there are qualitative and quantitative differences in the staining between benign prostatic hyperplasia tissues and prostate cancer tissues, suggesting that this polypeptide may be detected selectively in prostate tumors and therefore be useful  
25 in the diagnosis of prostate cancer.



## EXAMPLE 3

ISOLATION AND CHARACTERIZATION OF PROSTATE-SPECIFIC  
POLYPEPTIDES BY PCR-BASED SUBTRACTION

5           A cDNA subtraction library, containing cDNA from normal prostate subtracted with ten other normal tissue cDNAs (brain, heart, kidney, liver, lung, ovary, placenta, skeletal muscle, spleen and thymus) and then submitted to a first round of PCR amplification, was purchased from Clontech. This library was subjected to a second round of PCR amplification, following the manufacturer's protocol. The  
10   resulting cDNA fragments were subcloned into the vector pT7 Blue T-vector (Novagen, Madison, WI) and transformed into XL-1 Blue MRF' *E. coli* (Stratagene). DNA was isolated from independent clones and sequenced using a Perkin Elmer/Applied Biosystems Division Automated Sequencer Model 373A.

          Fifty-nine positive clones were sequenced. Comparison of the DNA  
15   sequences of these clones with those in the gene bank, as described above, revealed no significant homologies to 25 of these clones, hereinafter referred to as P5, P8, P9, P18, P20, P30, P34, P36, P38, P39, P42, P49, P50, P53, P55, P60, P64, P65, P73, P75, P76, P79 and P84. The determined cDNA sequences for these clones are provided in SEQ ID NO: 41-45, 47-52 and 54-65, respectively. P29, P47, P68, P80 and P82 (SEQ ID  
20   NO: 46, 53 and 66-68, respectively) were found to show some degree of homology to previously identified DNA sequences. To the best of the inventors' knowledge, none of these sequences have been previously shown to be present in prostate.

          Further studies employing the sequence of SEQ ID NO: 67 as a probe in standard full-length cloning methods, resulted in the isolation of three cDNA sequences  
25   which appear to be splice variants of P80 (also known as P704P). These sequences are provided in SEQ ID NO: 620-622.

          Further studies using the PCR-based methodology described above resulted in the isolation of more than 180 additional clones, of which 23 clones were found to show no significant homologies to known sequences. The determined cDNA  
30   sequences for these clones are provided in SEQ ID NO: 115-123, 127, 131, 137, 145,

147-151, 153, 156-158 and 160. Twenty-three clones (SEQ ID NO: 124-126, 128-130, 132-136, 138-144, 146, 152, 154, 155 and 159) were found to show some homology to previously identified ESTs. An additional ten clones (SEQ ID NO: 161-170) were found to have some degree of homology to known genes. Larger cDNA clones  
5 containing the P20 sequence represent splice variants of a gene referred to as P703P. The determined DNA sequence for the variants referred to as DE1, DE13 and DE14 are provided in SEQ ID NOS: 171, 175 and 177, respectively, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 172, 176 and 178, respectively. The determined cDNA sequence for an extended spliced form of P703 is  
10 provided in SEQ ID NO: 225. The DNA sequences for the splice variants referred to as DE2 and DE6 are provided in SEQ ID NOS: 173 and 174, respectively.

mRNA Expression levels for representative clones in tumor tissues (prostate (n=5), breast (n=2), colon and lung) normal tissues (prostate (n=5), colon, kidney, liver, lung (n=2), ovary (n=2), skeletal muscle, skin, stomach, small intestine  
15 and brain), and activated and non-activated PBMC was determined by RT-PCR as described above. Expression was examined in one sample of each tissue type unless otherwise indicated.

P9 was found to be highly expressed in normal prostate and prostate tumor compared to all normal tissues tested except for normal colon which showed  
20 comparable expression. P20, a portion of the P703P gene, was found to be highly expressed in normal prostate and prostate tumor, compared to all twelve normal tissues tested. A modest increase in expression of P20 in breast tumor (n=2), colon tumor and lung tumor was seen compared to all normal tissues except lung (1 of 2). Increased expression of P18 was found in normal prostate, prostate tumor and breast tumor  
25 compared to other normal tissues except lung and stomach. A modest increase in expression of P5 was observed in normal prostate compared to most other normal tissues. However, some elevated expression was seen in normal lung and PBMC. Elevated expression of P5 was also observed in prostate tumors (2 of 5), breast tumor and one lung tumor sample. For P30, similar expression levels were seen in normal  
30 prostate and prostate tumor, compared to six of twelve other normal tissues tested.

Increased expression was seen in breast tumors, one lung tumor sample and one colon tumor sample, and also in normal PBMC. P29 was found to be over-expressed in prostate tumor (5 of 5) and normal prostate (5 of 5) compared to the majority of normal tissues. However, substantial expression of P29 was observed in normal colon and  
5 normal lung (2 of 2). P80 was found to be over-expressed in prostate tumor (5 of 5) and normal prostate (5 of 5) compared to all other normal tissues tested, with increased expression also being seen in colon tumor.

Further studies resulted in the isolation of twelve additional clones, hereinafter referred to as 10-d8, 10-h10, 11-c8, 7-g6, 8-b5, 8-b6, 8-d4, 8-d9, 8-g3, 8-  
10 h11, 9-f12 and 9-f3. The determined DNA sequences for 10-d8, 10-h10, 11-c8, 8-d4, 8-d9, 8-h11, 9-f12 and 9-f3 are provided in SEQ ID NO: 207, 208, 209, 216, 217, 220, 221 and 222, respectively. The determined forward and reverse DNA sequences for 7-g6, 8-b5, 8-b6 and 8-g3 are provided in SEQ ID NO: 210 and 211; 212 and 213; 214 and 215; and 218 and 219, respectively. Comparison of these sequences with those in  
15 the gene bank revealed no significant homologies to the sequence of 9-f3. The clones 10-d8, 11-c8 and 8-h11 were found to show some homology to previously isolated ESTs, while 10-h10, 8-b5, 8-b6, 8-d4, 8-d9, 8-g3 and 9-f12 were found to show some homology to previously identified genes. Further characterization of 7-G6 and 8-G3 showed identity to the known genes PAP and PSA, respectively.

20 mRNA expression levels for these clones were determined using the micro-array technology described above. The clones 7-G6, 8-G3, 8-B5, 8-B6, 8-D4, 8-D9, 9-F3, 9-F12, 9-H3, 10-A2, 10-A4, 11-C9 and 11-F2 were found to be over-expressed in prostate tumor and normal prostate, with expression in other tissues tested being low or undetectable. Increased expression of 8-F11 was seen in prostate tumor  
25 and normal prostate, bladder, skeletal muscle and colon. Increased expression of 10-H10 was seen in prostate tumor and normal prostate, bladder, lung, colon, brain and large intestine. Increased expression of 9-B1 was seen in prostate tumor, breast tumor, and normal prostate, salivary gland, large intestine and skin, with increased expression of 11-C8 being seen in prostate tumor, and normal prostate and large intestine.

An additional cDNA fragment derived from the PCR-based normal prostate subtraction, described above, was found to be prostate specific by both microarray technology and RT-PCR. The determined cDNA sequence of this clone (referred to as 9-A11) is provided in SEQ ID NO: 226. Comparison of this sequence with those  
5 in the public databases revealed 99% identity to the known gene HOXB13.

Further studies led to the isolation of the clones 8-C6 and 8-H7. The determined cDNA sequences for these clones are provided in SEQ ID NO: 227 and 228, respectively. These sequences were found to show some homology to previously isolated ESTs.

10 PCR and hybridization-based methodologies were employed to obtain longer cDNA sequences for clone P20 (also referred to as P703P), yielding three additional cDNA fragments that progressively extend the 5' end of the gene. These fragments, referred to as P703PDE5, P703P6.26, and P703PX-23 (SEQ ID NO: 326, 328 and 330, with the predicted corresponding amino acid sequences being provided in  
15 SEQ ID NO: 327, 329 and 331, respectively) contain additional 5' sequence. P703PDE5 was recovered by screening of a cDNA library (#141-26) with a portion of P703P as a probe. P703P6.26 was recovered from a mixture of three prostate tumor cDNAs and P703PX\_23 was recovered from cDNA library (#438-48). Together, the additional sequences include all of the putative mature serine protease along with part of  
20 the putative signal sequence. The full-length cDNA sequence for P703P is provided in SEQ ID NO: 524, with the corresponding amino acid sequence being provided in SEQ ID NO: 525.

Using computer algorithms, the following regions of P703P were predicted to represent potential HLA A2-binding CTL epitopes: amino acids 164-172  
25 of SEQ ID NO: 525 (SEQ ID NO: 723); amino acids 160-168 of SEQ ID NO: 525 (SEQ ID NO: 724); amino acids 239-247 of SEQ ID NO: 525 (SEQ ID NO: 725); amino acids 118-126 of SEQ ID NO: 525 (SEQ ID NO: 726); amino acids 112-120 of SEQ ID NO: 525 (SEQ ID NO: 727); amino acids 155-164 of SEQ ID NO: 525 (SEQ ID NO: 728); amino acids 117-126 of SEQ ID NO: 525 (SEQ ID NO: 729); amino acids  
30 164-173 of SEQ ID NO: 525 (SEQ ID NO: 730); amino acids 154-163 of SEQ ID NO:

525 (SEQ ID NO: 731); amino acids 163-172 of SEQ ID NO: 525 (SEQ ID NO: 732); amino acids 58-66 of SEQ ID NO: 525 (SEQ ID NO: 733); and amino acids 59-67 of SEQ ID NO: 525 (SEQ ID NO: 734).

P703P was found to show some homology to previously identified proteases, such as thrombin. The thrombin receptor has been shown to be preferentially expressed in highly metastatic breast carcinoma cells and breast carcinoma biopsy samples. Introduction of thrombin receptor antisense cDNA has been shown to inhibit the invasion of metastatic breast carcinoma cells in culture. Antibodies against thrombin receptor inhibit thrombin receptor activation and thrombin-induced platelet activation. Furthermore, peptides that resemble the receptor's tethered ligand domain inhibit platelet aggregation by thrombin. P703P may play a role in prostate cancer through a protease-activated receptor on the cancer cell or on stromal cells. The potential trypsin-like protease activity of P703P may either activate a protease-activated receptor on the cancer cell membrane to promote tumorigenesis or activate a protease-activated receptor on the adjacent cells (such as stromal cells) to secrete growth factors and/or proteases (such as matrix metalloproteinases) that could promote tumor angiogenesis, invasion and metastasis. P703P may thus promote tumor progression and/or metastasis through the activation of protease-activated receptor. Polypeptides and antibodies that block the P703P-receptor interaction may therefore be usefully employed in the treatment of prostate cancer.

To determine whether P703P expression increases with increased severity of Gleason grade, an indicator of tumor stage, quantitative PCR analysis was performed on prostate tumor samples with a range of Gleason scores from 5 to > 8. The mean level of P703P expression increased with increasing Gleason score, indicating that P703P expression may correlate with increased disease severity.

Further studies using a PCR-based subtraction library of a prostate tumor pool subtracted against a pool of normal tissues (referred to as JP: PCR subtraction) resulted in the isolation of thirteen additional clones, seven of which did not share any significant homology to known GenBank sequences. The determined cDNA sequences for these seven clones (P711P, P712P, novel 23, P774P, P775P, P710P and P768P) are

provided in SEQ ID NO: 307-311, 313 and 315, respectively. The remaining six clones (SEQ ID NO: 316 and 321-325) were shown to share some homology to known genes. By microarray analysis, all thirteen clones showed three or more fold over-expression in prostate tissues, including prostate tumors, BPH and normal prostate as compared to normal non-prostate tissues. Clones P711P, P712P, novel 23 and P768P showed over-expression in most prostate tumors and BPH tissues tested (n=29), and in the majority of normal prostate tissues (n=4), but background to low expression levels in all normal tissues. Clones P774P, P775P and P710P showed comparatively lower expression and expression in fewer prostate tumors and BPH samples, with negative to low expression in normal prostate.

Further studies led to the isolation of an extended cDNA sequence for P712P (SEQ ID NO: 552). The amino acid sequences encoded by 16 predicted open reading frames present within the sequence of SEQ ID NO: 552 are provided in SEQ ID NO: 553-568.

The full-length cDNA for P711P was obtained by employing the partial sequence of SEQ ID NO: 307 to screen a prostate cDNA library. Specifically, a directionally cloned prostate cDNA library was prepared using standard techniques. One million colonies of this library were plated onto LB/Amp plates. Nylon membrane filters were used to lift these colonies, and the cDNAs which were picked up by these filters were denatured and cross-linked to the filters by UV light. The P711P cDNA fragment of SEQ ID NO: 307 was radio-labeled and used to hybridize with these filters. Positive clones were selected, and cDNAs were prepared and sequenced using an automatic Perkin Elmer/Applied Biosystems sequencer. The determined full-length sequence of P711P is provided in SEQ ID NO: 382, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 383.

Using PCR and hybridization-based methodologies, additional cDNA sequence information was derived for two clones described above, 11-C9 and 9-F3, herein after referred to as P707P and P714P, respectively (SEQ ID NO: 333 and 334). After comparison with the most recent GenBank, P707P was found to be a splice variant of the known gene HoxB13. In contrast, no significant homologies to P714P

were found. Further studies employing the sequence of SEQ ID NO: 334 as a probe in standard full-length cloning methods, resulted in an extended cDNA sequence for P714P. This sequence is provided in SEQ ID NO: 619. This sequence was found to show some homology to the gene that encodes human ribosomal L23A protein.

5 Clones 8-B3, P89, P98, P130 and P201 (as disclosed in U.S. Patent Application No. 09/020,956, filed February 9, 1998) were found to be contained within one contiguous sequence, referred to as P705P (SEQ ID NO: 335, with the predicted amino acid sequence provided in SEQ ID NO: 336), which was determined to be a splice variant of the known gene NKX 3.1.

10 Further studies on P775P resulted in the isolation of four additional sequences (SEQ ID NO: 473-476) which are all splice variants of the P775P gene. The sequence of SEQ ID NO: 474 was found to contain two open reading frames (ORFs). The predicted amino acid sequences encoded by these ORFs are provided in SEQ ID NO: 477 and 478. The cDNA sequence of SEQ ID NO: 475 was found to contain an  
15 ORF which encodes the amino acid sequence of SEQ ID NO: 479. The cDNA sequence of SEQ ID NO: 473 was found to contain four ORFs. The predicted amino acid sequences encoded by these ORFs are provided in SEQ ID NO: 480-483. Additional splice variants of P775P are provided in SEQ ID NO: 593-597.

Subsequent studies led to the identification of a genomic region on  
20 chromosome 22q11.2, known as the Cat Eye Syndrome region, that contains the five prostate genes P704P, P712P, P774P, P775P and B305D. The relative location of each of these five genes within the genomic region is shown in Fig. 10. This region may therefore be associated with malignant tumors, and other potential tumor genes may be contained within this region. These studies also led to the identification of a potential  
25 open reading frame (ORF) for P775P (provided in SEQ ID NO: 533), which encodes the amino acid sequence of SEQ ID NO: 534.

Comparison of the clone of SEQ ID NO: 325 (referred to as P558S) with sequences in the GenBank and GeneSeq DNA databases showed that P558S is identical to the prostate-specific transglutaminase gene, which is known to have two forms. The  
30 full-length sequences for the two forms are provided in SEQ ID NO: 630 and 631, with

the corresponding amino acid sequences being provided in SEQ ID NO: 632 and 633, respectively. The cDNA sequence of SEQ ID NO: 631 has a 15 pair base insert, resulting in a 5 amino acid insert in the corresponding amino acid sequence (SEQ ID NO: 633). This insert is not present in the sequence of SEQ ID NO: 630.

5 Further studies on P768P (SEQ ID NO: 315) led to the identification of the putative full-length open reading frame (ORF). The cDNA sequence of the ORF with stop codon is provided in SEQ ID NO: 764. The cDNA sequence of the ORF without stop codon is provided in SEQ ID NO: 765, with the corresponding amino acid sequence being provided in SEQ ID NO: 766. This sequence was found to show 86%  
10 identity to a rat calcium transporter protein, indicating that P768P may represent a human calcium transporter protein. The locations of transmembrane domains within P768P were predicted using the PSORT II computer algorithm. Six transmembrane domains were predicted at amino acid positions 118-134, 172-188, 211-227, 230-246, 282-298 and 348-364. The amino acid sequences of SEQ ID NO: 767-772 represent  
15 amino acids 1-134, 135-188, 189-227, 228-246, 247-298 and 299-511 of P768P, respectively.

#### EXAMPLE 4

##### SYNTHESIS OF POLYPEPTIDES

20

Polypeptides may be synthesized on a Perkin Elmer/Applied Biosystems 430A peptide synthesizer using Fmoc chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of  
25 conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid  
30 (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of



0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

5

## EXAMPLE 5

FURTHER ISOLATION AND CHARACTERIZATION OF  
PROSTATE-SPECIFIC POLYPEPTIDES BY PCR-BASED SUBTRACTION

10 A cDNA library generated from prostate primary tumor mRNA as described above was subtracted with cDNA from normal prostate. The subtraction was performed using a PCR-based protocol (Clontech), which was modified to generate larger fragments. Within this protocol, tester and driver double stranded cDNA were separately digested with five restriction enzymes that recognize six-nucleotide  
15 restriction sites (MluI, MscI, PvuII, SalI and StuI). This digestion resulted in an average cDNA size of 600 bp, rather than the average size of 300 bp that results from digestion with RsaI according to the Clontech protocol. This modification did not affect the subtraction efficiency. Two tester populations were then created with different adapters, and the driver library remained without adapters.

20 The tester and driver libraries were then hybridized using excess driver cDNA. In the first hybridization step, driver was separately hybridized with each of the two tester cDNA populations. This resulted in populations of (a) unhybridized tester cDNAs, (b) tester cDNAs hybridized to other tester cDNAs, (c) tester cDNAs hybridized to driver cDNAs and (d) unhybridized driver cDNAs. The two separate  
25 hybridization reactions were then combined, and rehybridized in the presence of additional denatured driver cDNA. Following this second hybridization, in addition to populations (a) through (d), a fifth population (e) was generated in which tester cDNA with one adapter hybridized to tester cDNA with the second adapter. Accordingly, the second hybridization step resulted in enrichment of differentially expressed sequences  
30 which could be used as templates for PCR amplification with adaptor-specific primers.

The ends were then filled in, and PCR amplification was performed using adaptor-specific primers. Only population (e), which contained tester cDNA that did not hybridize to driver cDNA, was amplified exponentially. A second PCR amplification step was then performed, to reduce background and further enrich  
5 differentially expressed sequences.

This PCR-based subtraction technique normalizes differentially expressed cDNAs so that rare transcripts that are overexpressed in prostate tumor tissue may be recoverable. Such transcripts would be difficult to recover by traditional subtraction methods.

10 In addition to genes known to be overexpressed in prostate tumor, seventy-seven further clones were identified. Sequences of these partial cDNAs are provided in SEQ ID NO: 29 to 305. Most of these clones had no significant homology to database sequences. Exceptions were JPTPN23 (SEQ ID NO: 231; similarity to pig valosin-containing protein), JPTPN30 (SEQ ID NO: 234; similarity to rat mRNA for  
15 proteasome subunit), JPTPN45 (SEQ ID NO: 243; similarity to rat *norvegicus* cytosolic NADP-dependent isocitrate dehydrogenase), JPTPN46 (SEQ ID NO: 244; similarity to human subclone H8 4 d4 DNA sequence), JP1D6 (SEQ ID NO: 265; similarity to *G. gallus* dynein light chain-A), JP8D6 (SEQ ID NO: 288; similarity to human BAC clone RG016J04), JP8F5 (SEQ ID NO: 289; similarity to human subclone H8 3 b5 DNA  
20 sequence), and JP8E9 (SEQ ID NO: 299; similarity to human Alu sequence).

Additional studies using the PCR-based subtraction library consisting of a prostate tumor pool subtracted against a normal prostate pool (referred to as PT-PN PCR subtraction) yielded three additional clones. Comparison of the cDNA sequences of these clones with the most recent release of GenBank revealed no significant  
25 homologies to the two clones referred to as P715P and P767P (SEQ ID NO: 312 and 314). The remaining clone was found to show some homology to the known gene KIAA0056 (SEQ ID NO: 318). Using microarray analysis to measure mRNA expression levels in various tissues, all three clones were found to be over-expressed in prostate tumors and BPH tissues. Specifically, clone P715P was over-expressed in most  
30 prostate tumors and BPH tissues by a factor of three or greater, with elevated expression

seen in the majority of normal prostate samples and in fetal tissue, but negative to low expression in all other normal tissues. Clone P767P was over-expressed in several prostate tumors and BPH tissues, with moderate expression levels in half of the normal prostate samples, and background to low expression in all other normal tissues tested.

5 Further analysis, by microarray as described above, of the PT-PN PCR subtraction library and of a DNA subtraction library containing cDNA from prostate tumor subtracted with a pool of normal tissue cDNAs, led to the isolation of 27 additional clones (SEQ ID NO: 340-365 and 381) which were determined to be over-expressed in prostate tumor. The clones of SEQ ID NO: 341, 342, 345, 347, 348, 349,  
10 351, 355-359, 361, 362 and 364 were also found to be expressed in normal prostate. Expression of all 26 clones in a variety of normal tissues was found to be low or undetectable, with the exception of P544S (SEQ ID NO: 356) which was found to be expressed in small intestine. Of the 26 clones, 11 (SEQ ID NO: 340-349 and 362) were found to show some homology to previously identified sequences. No significant  
15 homologies were found to the clones of SEQ ID NO: 350, 351, 353-361, and 363-365.

Comparison of the sequence of SEQ ID NO: 362 with sequences in the GenBank and GeneSeq DNA databases showed that this clone (referred to as P788P) is identical to GeneSeq Accession No. X27262, which encodes a protein found in the GeneSeq protein Accession No. Y00931. The full length cDNA sequence of P788P is  
20 provided in SEQ ID NO: 634, with the corresponding predicted amino acid being provided in SEQ ID NO: 635. Subsequently, a full-length cDNA sequence for P788P that contains polymorphisms not found in the sequence of SEQ ID NO: 634, was cloned multiple times by PCR amplification from cDNA prepared from several RNA templates from three individuals. This determined cDNA sequence of this polymorphic variant of  
25 P788P is provided in SEQ ID NO: 636, with the corresponding amino acid sequence being provided in SEQ ID NO: 637. The sequence of SEQ ID NO: 637 differs from that of SEQ ID NO: 635 by six amino acid residues. The P788P protein has 7 potential transmembrane domains at the C-terminal portion and is predicted to be a plasma membrane protein with an extracellular N-terminal region.

Further studies on the clone of SEQ ID NO: 352 (referred to as P790P) led to the isolation of the full-length cDNA sequence of SEQ ID NO: 526. The corresponding predicted amino acid is provided in SEQ ID NO: 527. Data from two quantitative PCR experiments indicated that P790P is over-expressed in 11/15 tested prostate tumor samples and is expressed at low levels in spinal cord, with no expression being seen in all other normal samples tested. Data from further PCR experiments and microarray experiments showed over-expression in normal prostate and prostate tumor with little or no expression in other tissues tested. P790P was subsequently found to show significant homology to a previously identified G-protein coupled prostate tissue receptor.

Additional studies on the clone of SEQ ID NO: 354 (referred to as P776P) led to the isolation of an extended cDNA sequence, provided in SEQ ID NO: 569. The determined cDNA sequences of three additional splice variants of P776P are provided in SEQ ID NO: 570-572. The amino acid sequences encoded by two predicted open reading frames (ORFs) contained within SEQ ID NO: 570, one predicted ORF contained within SEQ ID NO: 571, and 11 predicted ORFs contained within SEQ ID NO: 569, are provided in SEQ ID NO: 573-586, respectively. Further studies led to the isolation of the full-length sequence for the clone of SEQ ID NO: 570 (provided in SEQ ID NO: 737). Full-length cloning efforts on the clone of SEQ ID NO: 571 led to the isolation of two sequences (provided in SEQ ID NO: 738 and 739), representing a single clone, that are identical with the exception of a polymorphic insertion/deletion at position 1293. Specifically, the clone of SEQ ID NO: 739 (referred to as clone F1) has a C at position 1293. The clone of SEQ ID NO: 738 (referred to as clone F2) has a single base pair deletion at position 1293. The predicted amino acid sequences encoded by 5 open reading frames located within SEQ ID NO: 737 are provided in SEQ ID NO: 740-744, with the predicted amino acid sequences encoded by the clone of SEQ ID NO: 738 and 739 being provided in SEQ ID NO: 745-750.

Comparison of the cDNA sequences for the clones P767P (SEQ ID NO: 314) and P777P (SEQ ID NO: 350) with sequences in the GenBank human EST database showed that the two clones matched many EST sequences in common,

suggesting that P767P and P777P may represent the same gene. A DNA consensus sequence derived from a DNA sequence alignment of P767P, P777P and multiple EST clones is provided in SEQ ID NO: 587. The amino acid sequences encoded by three putative ORFs located within SEQ ID NO: 587 are provided in SEQ ID NO: 588-590.

5           The clone of SEQ ID NO: 342 (referred to as P789P) was found to show homology to a previously identified gene. The full length cDNA sequence for P789P and the corresponding amino acid sequence are provided in SEQ ID NO: 735 and 736, respectively.

10

## EXAMPLE 6

### PEPTIDE PRIMING OF MICE AND PROPAGATION OF CTL LINES

6.1. This Example illustrates the preparation of a CTL cell line specific for cells expressing the P502S gene.

15           Mice expressing the transgene for human HLA A2Kb (provided by Dr L. Sherman, The Scripps Research Institute, La Jolla, CA) were immunized with P2S#12 peptide (VLGWVAEL; SEQ ID NO: 306), which is derived from the P502S gene (also referred to herein as J1-17, SEQ ID NO: 8), as described by Theobald et al., *Proc. Natl. Acad. Sci. USA* 92:11993-11997, 1995 with the following modifications. Mice were  
20 immunized with 100µg of P2S#12 and 120µg of an I-A<sup>b</sup> binding peptide derived from hepatitis B Virus protein emulsified in incomplete Freund's adjuvant. Three weeks later these mice were sacrificed and using a nylon mesh single cell suspensions prepared. Cells were then resuspended at  $6 \times 10^6$  cells/ml in complete media (RPMI-1640; Gibco BRL, Gaithersburg, MD) containing 10% FCS, 2mM Glutamine (Gibco BRL), sodium  
25 pyruvate (Gibco BRL), non-essential amino acids (Gibco BRL),  $2 \times 10^{-5}$  M 2-mercaptoethanol, 50U/ml penicillin and streptomycin, and cultured in the presence of irradiated (3000 rads) P2S#12-pulsed (5mg/ml P2S#12 and 10mg/ml  $\beta$ 2-microglobulin) LPS blasts (A2 transgenic spleens cells cultured in the presence of 7µg/ml dextran sulfate and 25µg/ml LPS for 3 days). Six days later, cells ( $5 \times 10^5$ /ml) were  
30 restimulated with  $2.5 \times 10^6$ /ml peptide pulsed irradiated (20,000 rads) EL4A2Kb cells

(Sherman et al, *Science* 258:815-818, 1992) and  $3 \times 10^6$ /ml A2 transgenic spleen feeder cells. Cells were cultured in the presence of 20U/ml IL-2. Cells continued to be restimulated on a weekly basis as described, in preparation for cloning the line.

P2S#12 line was cloned by limiting dilution analysis with peptide pulsed  
5 EL4 A2Kb tumor cells ( $1 \times 10^4$  cells/ well) as stimulators and A2 transgenic spleen cells as feeders ( $5 \times 10^5$  cells/ well) grown in the presence of 30U/ml IL-2. On day 14, cells were restimulated as before. On day 21, clones that were growing were isolated and maintained in culture. Several of these clones demonstrated significantly higher reactivity (lysis) against human fibroblasts (HLA A2Kb expressing) transduced with  
10 P502S than against control fibroblasts. An example is presented in Figure 1.

This data indicates that P2S #12 represents a naturally processed epitope of the P502S protein that is expressed in the context of the human HLA A2Kb molecule.

15 6.2. This Example illustrates the preparation of murine CTL lines and CTL clones specific for cells expressing the P501S gene.

This series of experiments were performed similarly to that described above. Mice were immunized with the P1S#10 peptide (SEQ ID NO: 337), which is  
20 derived from the P501S gene (also referred to herein as L1-12, SEQ ID NO: 110). The P1S#10 peptide was derived by analysis of the predicted polypeptide sequence for P501S for potential HLA-A2 binding sequences as defined by published HLA-A2 binding motifs (Parker, KC, et al, *J. Immunol.*, 152:163, 1994). P1S#10 peptide was synthesized as described in Example 4, and empirically tested for HLA-A2 binding  
25 using a T cell based competition assay. Predicted A2 binding peptides were tested for their ability to compete HLA-A2 specific peptide presentation to an HLA-A2 restricted CTL clone (D150M58), which is specific for the HLA-A2 binding influenza matrix peptide fluM58. D150M58 CTL secretes TNF in response to self-presentation of peptide fluM58. In the competition assay, test peptides at 100-200  $\mu$ g/ml were added to  
30 cultures of D150M58 CTL in order to bind HLA-A2 on the CTL. After thirty minutes,

CTL cultured with test peptides, or control peptides, were tested for their antigen dose response to the fluM58 peptide in a standard TNF bioassay. As shown in Figure 3, peptide P1S#10 competes HLA-A2 restricted presentation of fluM58, demonstrating that peptide P1S#10 binds HLA-A2.

- 5 Mice expressing the transgene for human HLA A2Kb were immunized as described by Theobald et al. (*Proc. Natl. Acad. Sci. USA* 92:11993-11997, 1995) with the following modifications. Mice were immunized with 62.5 $\mu$ g of P1S #10 and 120 $\mu$ g of an I-A<sup>b</sup> binding peptide derived from Hepatitis B Virus protein emulsified in incomplete Freund's adjuvant. Three weeks later these mice were sacrificed and single  
10 cell suspensions prepared using a nylon mesh. Cells were then resuspended at  $6 \times 10^6$  cells/ml in complete media (as described above) and cultured in the presence of irradiated (3000 rads) P1S#10-pulsed (2 $\mu$ g/ml P1S#10 and 10mg/ml  $\beta$ 2-microglobulin) LPS blasts (A2 transgenic spleens cells cultured in the presence of 7 $\mu$ g/ml dextran sulfate and 25 $\mu$ g/ml LPS for 3 days). Six days later cells ( $5 \times 10^5$ /ml) were restimulated  
15 with  $2.5 \times 10^6$ /ml peptide-pulsed irradiated (20,000 rads) EL4A2Kb cells, as described above, and  $3 \times 10^6$ /ml A2 transgenic spleen feeder cells. Cells were cultured in the presence of 20 U/ml IL-2. Cells were restimulated on a weekly basis in preparation for cloning. After three rounds of *in vitro* stimulations, one line was generated that recognized P1S#10-pulsed Jurkat A2Kb targets and P501S-transduced Jurkat targets as  
20 shown in Figure 4.

- A P1S#10-specific CTL line was cloned by limiting dilution analysis with peptide pulsed EL4 A2Kb tumor cells ( $1 \times 10^4$  cells/ well) as stimulators and A2 transgenic spleen cells as feeders ( $5 \times 10^5$  cells/ well) grown in the presence of 30U/ml IL-2. On day 14, cells were restimulated as before. On day 21, viable clones were  
25 isolated and maintained in culture. As shown in Figure 5, five of these clones demonstrated specific cytolytic reactivity against P501S-transduced Jurkat A2Kb targets. This data indicates that P1S#10 represents a naturally processed epitope of the P501S protein that is expressed in the context of the human HLA-A2.1 molecule.

## EXAMPLE 7

PRIMING OF CTL *IN VIVO* USING NAKED DNA IMMUNIZATION

## WITH A PROSTATE ANTIGEN

The prostate-specific antigen L1-12, as described above, is also referred  
5 to as P501S. HLA A2Kb Tg mice (provided by Dr L. Sherman, The Scripps Research  
Institute, La Jolla, CA) were immunized with 100 µg P501S in the vector VR1012  
either intramuscularly or intradermally. The mice were immunized three times, with a  
two week interval between immunizations. Two weeks after the last immunization,  
immune spleen cells were cultured with Jurkat A2Kb-P501S transduced stimulator  
10 cells. CTL lines were stimulated weekly. After two weeks of *in vitro* stimulation, CTL  
activity was assessed against P501S transduced targets. Two out of 8 mice developed  
strong anti-P501S CTL responses. These results demonstrate that P501S contains at  
least one naturally processed HLA-A2-restricted CTL epitope.

15

## EXAMPLE 8

## ABILITY OF HUMAN T CELLS TO RECOGNIZE PROSTATE-SPECIFIC POLYPEPTIDES

This Example illustrates the ability of T cells specific for a prostate  
tumor polypeptide to recognize human tumor.

20 Human CD8<sup>+</sup> T cells were primed *in vitro* to the P2S-12 peptide (SEQ  
ID NO: 306) derived from P502S (also referred to as J1-17) using dendritic cells  
according to the protocol of Van Tsai et al. (*Critical Reviews in Immunology* 18:65-75,  
1998). The resulting CD8<sup>+</sup> T cell microcultures were tested for their ability to  
recognize the P2S-12 peptide presented by autologous fibroblasts or fibroblasts which  
25 were transduced to express the P502S gene in a  $\gamma$ -interferon ELISPOT assay (see  
Lalvani et al., *J. Exp. Med.* 186:859-865, 1997). Briefly, titrating numbers of T cells  
were assayed in duplicate on 10<sup>4</sup> fibroblasts in the presence of 3 µg/ml human  $\beta_2$ -  
microglobulin and 1 µg/ml P2S-12 peptide or control E75 peptide. In addition, T cells  
were simultaneously assayed on autologous fibroblasts transduced with the P502S gene  
30 or as a control, fibroblasts transduced with HER-2/*neu*. Prior to the assay, the



fibroblasts were treated with 10 ng/ml  $\gamma$ -interferon for 48 hours to upregulate class I MHC expression. One of the microcultures (#5) demonstrated strong recognition of both peptide pulsed fibroblasts as well as transduced fibroblasts in a  $\gamma$ -interferon ELISPOT assay. Figure 2A demonstrates that there was a strong increase in the number of  $\gamma$ -interferon spots with increasing numbers of T cells on fibroblasts pulsed with the P2S-12 peptide (solid bars) but not with the control E75 peptide (open bars). This shows the ability of these T cells to specifically recognize the P2S-12 peptide. As shown in Figure 2B, this microculture also demonstrated an increase in the number of  $\gamma$ -interferon spots with increasing numbers of T cells on fibroblasts transduced to express the P502S gene but not the HER-2/*neu* gene. These results provide additional confirmatory evidence that the P2S-12 peptide is a naturally processed epitope of the P502S protein. Furthermore, this also demonstrates that there exists in the human T cell repertoire, high affinity T cells which are capable of recognizing this epitope. These T cells should also be capable of recognizing human tumors which express the P502S gene.

#### EXAMPLE 9

##### ELICITATION OF PROSTATE ANTIGEN-SPECIFIC CTL RESPONSES

##### IN HUMAN BLOOD

This Example illustrates the ability of a prostate-specific antigen to elicit a CTL response in blood of normal humans.

Autologous dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal donors by growth for five days in RPMI medium containing 10% human serum, 50 ng/ml GMCSF and 30 ng/ml IL-4. Following culture, DC were infected overnight with recombinant P501S-expressing vaccinia virus at an M.O.I. of 5 and matured for 8 hours by the addition of 2 micrograms/ml CD40 ligand. Virus was inactivated by UV irradiation, CD8<sup>+</sup> cells were isolated by positive selection using magnetic beads, and priming cultures were initiated in 24-well plates. Following five stimulation cycles using autologous fibroblasts

retrovirally transduced to express P501S and CD80, CD8+ lines were identified that specifically produced interferon-gamma when stimulated with autologous P501S-transduced fibroblasts. The P501S-specific activity of cell line 3A-1 could be maintained following additional stimulation cycles on autologous B-LCL transduced with P501S. Line 3A-1 was shown to specifically recognize autologous B-LCL transduced to express P501S, but not EGFP-transduced autologous B-LCL, as measured by cytotoxicity assays ( $^{51}\text{Cr}$  release) and interferon-gamma production (Interferon-gamma Elispot; *see above and Lalvani et al., J. Exp. Med. 186:859-865, 1997*). The results of these assays are presented in Figures 6A and 6B.

10

## EXAMPLE 10

IDENTIFICATION OF A NATURALLY PROCESSED CTL EPITOPE CONTAINED WITHIN THE  
PROSTATE-SPECIFIC ANTIGEN P703P

The 9-mer peptide p5 (SEQ ID NO: 338) was derived from the P703P antigen (also referred to as P20). The p5 peptide is immunogenic in human HLA-A2 donors and is a naturally processed epitope. Antigen specific human CD8+ T cells can be primed following repeated *in vitro* stimulations with monocytes pulsed with p5 peptide. These CTL specifically recognize p5-pulsed and P703P-transduced target cells in both ELISPOT (as described above) and chromium release assays. Additionally, immunization of HLA-A2Kb transgenic mice with p5 leads to the generation of CTL lines which recognize a variety of HLA-A2Kb or HLA-A2 transduced target cells expressing P703P.

Initial studies demonstrating that p5 is a naturally processed epitope were done using HLA-A2Kb transgenic mice. HLA-A2Kb transgenic mice were immunized subcutaneously in the footpad with 100  $\mu\text{g}$  of p5 peptide together with 140  $\mu\text{g}$  of hepatitis B virus core peptide (a Th peptide) in Freund's incomplete adjuvant. Three weeks post immunization, spleen cells from immunized mice were stimulated *in vitro* with peptide-pulsed LPS blasts. CTL activity was assessed by chromium release assay five days after primary *in vitro* stimulation. Retrovirally transduced cells expressing the

control antigen P703P and HLA-A2Kb were used as targets. CTL lines that specifically recognized both p5-pulsed targets as well as P703P-expressing targets were identified.

Human *in vitro* priming experiments demonstrated that the p5 peptide is immunogenic in humans. Dendritic cells (DC) were differentiated from monocyte  
5 cultures derived from PBMC of normal human donors by culturing for five days in RPMI medium containing 10% human serum, 50 ng/ml human GM-CSF and 30 ng/ml human IL-4. Following culture, the DC were pulsed with 1 ug/ml p5 peptide and cultured with CD8+ T cell enriched PBMC. CTL lines were restimulated on a weekly basis with p5-pulsed monocytes. Five to six weeks after initiation of the CTL cultures,  
10 CTL recognition of p5-pulsed target cells was demonstrated. CTL were additionally shown to recognize human cells transduced to express P703P, demonstrating that p5 is a naturally processed epitope.

Studies identifying a further peptide epitope (referred to as peptide 4) derived from the prostate tumor-specific antigen P703P that is capable of being  
15 recognized by CD4 T cells on the surface of cells in the context of HLA class II molecules were carried out as follows. The amino acid sequence for peptide 4 is provided in SEQ ID NO: 638, with the corresponding cDNA sequence being provided in SEQ ID NO: 639.

Twenty 15-mer peptides overlapping by 10 amino acids and derived  
20 from the carboxy-terminal fragment of P703P were generated using standard procedures. Dendritic cells (DC) were derived from PBMC of a normal female donor using GM-CSF and IL-4 by standard protocols. CD4 T cells were generated from the same donor as the DC using MACS beads and negative selection. DC were pulsed overnight with pools of the 15-mer peptides, with each peptide at a final concentration  
25 of 0.25 microgram/ml. Pulsed DC were washed and plated at  $1 \times 10^4$  cells/well of 96-well V-bottom plates and purified CD4 T cells were added at  $1 \times 10^5$ /well. Cultures were supplemented with 60 ng/ml IL-6 and 10 ng/ml IL-12 and incubated at 37 °C. Cultures were restimulated as above on a weekly basis using DC generated and pulsed as above as antigen presenting cells, supplemented with 5 ng/ml IL-7 and 10 u/ml IL-2.  
30 Following 4 *in vitro* stimulation cycles, 96 lines (each line corresponding to one well) were tested for specific proliferation and cytokine production in response to the

stimulating pools with an irrelevant pool of peptides derived from mammaglobin being used as a control.

One line (referred to as 1-F9) was identified from pool #1 that demonstrated specific proliferation (measured by <sup>3</sup>H proliferation assays) and cytokine production (measured by interferon-gamma ELISA assays) in response to pool #1 of P703P peptides. This line was further tested for specific recognition of the peptide pool, specific recognition of individual peptides in the pool, and in HLA mismatch analyses to identify the relevant restricting allele. Line 1-F9 was found to specifically proliferate and produce interferon-gamma in response to peptide pool #1, and also to peptide 4 (SEQ ID NO: 638). Peptide 4 corresponds to amino acids 126-140 of SEQ ID NO: 327. Peptide titration experiments were conducted to assess the sensitivity of line 1-F9 for the specific peptide. The line was found to specifically respond to peptide 4 at concentrations as low as 0.25 ng/ml, indicating that the T cells are very sensitive and therefore likely to have high affinity for the epitope.

To determine the HLA restriction of the P703P response, a panel of antigen presenting cells (APC) was generated that was partially matched with the donor used to generate the T cells. The APC were pulsed with the peptide and used in proliferation and cytokine assays together with line 1-F9. APC matched with the donor at HLA-DRB0701 and HLA-DQB02 alleles were able to present the peptide to the T cells, indicating that the P703P-specific response is restricted to one of these alleles.

Antibody blocking assays were utilized to determine if the restricting allele was HLA-DR0701 or HLA-DQ02. The anti-HLA-DR blocking antibody L243 or an irrelevant isotype matched IgG2a were added to T cells and APC cultures pulsed with the peptide RMPTVLQCVNVS VVS (SEQ ID NO: 638) at 250 ng/ml. Standard interferon-gamma and proliferation assays were performed. Whereas the control antibody had no effect on the ability of the T cells to recognize peptide-pulsed APC, in both assays the anti-HLA-DR antibody completely blocked the ability of the T cells to specifically recognize peptide-pulsed APC.

To determine if the peptide epitope RMPTVLQCVNVS VVS (SEQ ID NO: 638) was naturally processed, the ability of line 1-F9 to recognize APC pulsed with recombinant P703P protein was examined. For these experiments a number of

recombinant P703P sources were utilized; *E. coli*-derived P703P, Pichia-derived P703P and baculovirus-derived P703P. Irrelevant protein controls used were *E. coli*-derived L3E (a lung-specific antigen) and baculovirus-derived mammaglobin. In interferon-gamma ELISA assays, line 1-F9 was able to efficiently recognize both *E. coli* forms of P703P as well as Pichia-derived recombinant P703P, while baculovirus-derived P703P was recognized less efficiently. Subsequent Western blot analysis revealed that the *E. coli* and Pichia P703P protein preparations were intact while the baculovirus P703P preparation was approximately 75% degraded. Thus, peptide RMPTVLQCVNVS VVS (SEQ ID NO: 638) from P703P is a naturally processed peptide epitope derived from P703P and presented to T cells in the context of HLA-DRB-0701

In further studies, twenty-four 15-mer peptides overlapping by 10 amino acids and derived from the N-terminal fragment of P703P (corresponding to amino acids 27-154 of SEQ ID NO: 525) were generated by standard procedures and their ability to be recognized by CD4 cells was determined essentially as described above. DC were pulsed overnight with pools of the peptides with each peptide at a final concentration of 10 microgram/ml. A large number of individual CD4 T cell lines (65/480) demonstrated significant proliferation and cytokine release (IFN-gamma) in response to the P703P peptide pools but not to a control peptide pool. The CD4 T cell lines which demonstrated specific activity were restimulated on the appropriate pool of P703P peptides and reassayed on the individual peptides of each pool as well as a peptide dose titration of the pool of peptides in a IFN-gamma release assay and in a proliferation assay.

Sixteen immunogenic peptides were recognized by the T cells from the entire set of peptide antigens tested. The amino acid sequences of these peptides are provided in SEQ ID NO: 656-671, with the corresponding cDNA sequences being provided in SEQ ID NO: 640-655, respectively. In some cases the peptide reactivity of the T cell line could be mapped to a single peptide, however some could be mapped to more than one peptide in each pool. Those CD4 T cell lines that displayed a representative pattern of recognition from each peptide pool with a reasonable affinity for peptide were chosen for further analysis (I-1A, -6A; II-4C, -5E; III-6E, IV-4B, -3F, -9B, -10F, V-5B, -4D, and -10F). These CD4 T cell lines were restimulated on the

appropriate individual peptide and reassayed on autologous DC pulsed with a truncated form of recombinant P703P protein made in *E. coli* (a.a. 96 - 254 of SEQ ID NO: 525), full-length P703P made in the baculovirus expression system, and a fusion between influenza virus NS1 and P703P made in *E. coli*. Of the T cell lines tested, line I-1A  
5 recognized specifically the truncated form of P703P (*E. coli*) but no other recombinant form of P703P. This line also recognized the peptide used to elicit the T cells. Line 2-4C recognized the truncated form of P703P (*E. coli*) and the full length form of P703P made in baculovirus, as well as peptide. The remaining T cell lines tested were either peptide-specific only (II-5E, II-6F, IV-4B, IV-3F, IV-9B, IV-10F, V-5B and V-4D) or  
10 were non-responsive to any antigen tested (V-10F). These results demonstrate that the peptide sequence RPLLANDLMLIKLDE (SEQ ID NO: 671; corresponding to a.a. 110-124 of SEQ ID NO: 525) recognized by the T cell line I-1A, and the peptide sequences SVSESDTIRSISIAS (SEQ ID NO: 668; corresponding to a.a. 125-139 of SEQ ID NO: 525) and ISIASQCPTAGNSCL (SEQ ID NO: 667; corresponding to a.a. 135-149 of  
15 SEQ ID NO: 525) recognized by the T cell line II-4C may be naturally processed epitopes of the P703P protein.

### EXAMPLE 11

#### EXPRESSION OF A BREAST TUMOR-DERIVED ANTIGEN

20

#### IN PROSTATE

Isolation of the antigen B305D from breast tumor by differential display is described in US Patent Application No. 08/700,014, filed August 20, 1996. Several different splice forms of this antigen were isolated. The determined cDNA sequences  
25 for these splice forms are provided in SEQ ID NO: 366-375, with the predicted amino acid sequences corresponding to the sequences of SEQ ID NO: 292, 298 and 301-303 being provided in SEQ ID NO: 299-306, respectively. In further studies, a splice variant of the cDNA sequence of SEQ ID NO: 366 was isolated which was found to contain an additional guanine residue at position 884 (SEQ ID NO: 530), leading to a  
30 frameshift in the open reading frame. The determined DNA sequence of this ORF is

provided in SEQ ID NO: 531. This frameshift generates a protein sequence (provided in SEQ ID NO: 532) of 293 amino acids that contains the C-terminal domain common to the other isoforms of B305D but that differs in the N-terminal region.

The expression levels of B305D in a variety of tumor and normal tissues were examined by real time PCR and by Northern analysis. The results indicated that B305D is highly expressed in breast tumor, prostate tumor, normal prostate and normal testes, with expression being low or undetectable in all other tissues examined (colon tumor, lung tumor, ovary tumor, and normal bone marrow, colon, kidney, liver, lung, ovary, skin, small intestine, stomach). Using real-time PCR on a panel of prostate tumors, expression of B305D in prostate tumors was shown to increase with increasing Gleason grade, demonstrating that expression of B305D increases as prostate cancer progresses.

#### EXAMPLE 12

##### 15 GENERATION OF HUMAN CTL *IN VITRO* USING WHOLE GENE PRIMING AND STIMULATION TECHNIQUES WITH THE PROSTATE-SPECIFIC ANTIGEN P501S

Using *in vitro* whole-gene priming with P501S-vaccinia infected DC (see, for example, Yee et al, *The Journal of Immunology*, 157(9):4079-86, 1996), human CTL lines were derived that specifically recognize autologous fibroblasts transduced with P501S (also known as L1-12), as determined by interferon- $\gamma$  ELISPOT analysis as described above. Using a panel of HLA-mismatched B-LCL lines transduced with P501S, these CTL lines were shown to be likely restricted to HLAB class I allele. Specifically, dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal human donors by growing for five days in RPMI medium containing 10% human serum, 50 ng/ml human GM-CSF and 30 ng/ml human IL-4. Following culture, DC were infected overnight with recombinant P501S vaccinia virus at a multiplicity of infection (M.O.I) of five, and matured overnight by the addition of 3  $\mu$ g/ml CD40 ligand. Virus was inactivated by UV irradiation. CD8+ T cells were isolated using a magnetic bead system, and priming cultures were initiated

using standard culture techniques. Cultures were restimulated every 7-10 days using autologous primary fibroblasts retrovirally transduced with P501S and CD80. Following four stimulation cycles, CD8<sup>+</sup> T cell lines were identified that specifically produced interferon- $\gamma$  when stimulated with P501S and CD80-transduced autologous  
5 fibroblasts. A panel of HLA-mismatched B-LCL lines transduced with P501S were generated to define the restriction allele of the response. By measuring interferon- $\gamma$  in an ELISPOT assay, the P501S specific response was shown to be likely restricted by HLA B alleles. These results demonstrate that a CD8<sup>+</sup> CTL response to P501S can be elicited.

10 To identify the epitope(s) recognized, cDNA encoding P501S was fragmented by various restriction digests, and sub-cloned into the retroviral expression vector pBIB-KS. Retroviral supernatants were generated by transfection of the helper packaging line Phoenix-Ampho. Supernatants were then used to transduce Jurkat/A2Kb cells for CTL screening. CTL were screened in IFN-gamma ELISPOT  
15 assays against these A2Kb targets transduced with the "library" of P501S fragments. Initial positive fragments P501S/H3 and P501S/F2 were sequenced and found to encode amino acids 106-553 and amino acids 136-547, respectively, of SEQ ID NO: 113. A truncation of H3 was made to encode amino acid residues 106-351 of SEQ ID NO: 113, which was unable to stimulate the CTL, thus localizing the epitope to amino acid  
20 residues 351-547. Additional fragments encoding amino acids 1-472 (Fragment A) and amino acids 1-351 (Fragment B) were also constructed. Fragment A but not Fragment B stimulated the CTL thus localizing the epitope to amino acid residues 351-472. Overlapping 20-mer and 18-mer peptides representing this region were tested by pulsing Jurkat/A2Kb cells versus CTL in an IFN-gamma assay. Only peptides P501S-369(20)  
25 and P501S-369(18) stimulated the CTL. Nine-mer and 10-mer peptides representing this region were synthesized and similarly tested. Peptide P501S-370 (SEQ ID NO: 539) was the minimal 9-mer giving a strong response. Peptide P501S-376 (SEQ ID NO: 540) also gave a weak response, suggesting that it might represent a cross-reactive epitope.



In subsequent studies, the ability of primary human B cells transduced with P501S to prime MHC class I-restricted, P501S-specific, autologous CD8 T cells was examined. Primary B cells were derived from PBMC of a homozygous HLA-A2 donor by culture in CD40 ligand and IL-4, transduced at high frequency with recombinant P501S in the vector pBIB, and selected with blastocidin-S. For *in vitro* priming, purified CD8+ T cells were cultured with autologous CD40 ligand + IL-4 derived, P501S-transduced B cells in a 96-well microculture format. These CTL microcultures were re-stimulated with P501S-transduced B cells and then assayed for specificity. Following this initial screen, microcultures with significant signal above background were cloned on autologous EBV-transformed B cells (BLCL), also transduced with P501S. Using IFN-gamma ELISPOT for detection, several of these CD8 T cell clones were found to be specific for P501S, as demonstrated by reactivity to BLCL/P501S but not BLCL transduced with control antigen. It was further demonstrated that the anti-P501S CD8 T cell specificity is HLA-A2-restricted. First, antibody blocking experiments with anti-HLA-A,B,C monoclonal antibody (W6.32), anti-HLA-B,C monoclonal antibody (B1.23.2) and a control monoclonal antibody showed that only the anti-HLA-A,B,C antibody blocked recognition of P501S-expressing autologous BLCL. Secondly, the anti-P501S CTL also recognized an HLA-A2 matched, heterologous BLCL transduced with P501S, but not the corresponding EGFP transduced control BLCL.

A naturally processed, CD8, class I-restricted peptide epitope of P501S was identified as follows. Dendritic Cells (DC) were isolated by Percol gradient followed by differential adherence, and cultured for 5 days in the presence of RPMI medium containing 1% human serum, 50ng/ml GM-CSF and 30ng/ml IL-4. Following culture, DC were infected for 24 hours with P501S-expressing adenovirus at an MOI of 10 and matured for an additional 24 hours by the addition of 2ug/ml CD40 ligand. CD8 cells were enriched for by the subtraction of CD4+, CD14+ and CD16+ populations from PBMC with magnetic beads. Priming cultures containing 10,000 P501S-expressing DC and 100,000 CD8+ T cells per well were set up in 96-well V-bottom plates with RPMI containing 10% human serum, 5ng/ml IL-12 and 10ng/ml IL-6. Cultures were stimulated every 7 days using autologous fibroblasts retrovirally

transduced to express P501S and CD80, and were treated with IFN-gamma for 48-72 hours to upregulate MHC Class I expression. 10u/ml IL-2 was added at the time of stimulation and on days 2 and 5 following stimulation. Following 4 stimulation cycles, one P501S-specific CD8+ T cell line (referred to as 2A2) was identified that produced  
5 IFN-gamma in response to IFN-gamma-treated P501S/CD80 expressing autologous fibroblasts, but not in response to IFN-gamma-treated P703P/CD80 expressing autologous fibroblasts in a  $\gamma$ -IFN Elispot assay. Line 2A2 was cloned in 96-well plates with 0.5 cell/well or 2 cells/well in the presence of 75,000 PBMC/well, 10,000 B-LCL/well, 30ng/ml OKT3 and 50u/ml IL-2. Twelve clones were isolated that showed  
10 strong P501S specificity in response to transduced fibroblasts.

Fluorescence activated cell sorting (FACS) analysis was performed on P501S-specific clones using CD3-, CD4- and CD8-specific antibodies conjugated to PercP, FITC and PE respectively. Consistent with the use of CD8 enriched T cells in the priming cultures, P5401S-specific clones were determined to be CD3+, CD8+ and  
15 CD4-.

To identify the relevant P501S epitope recognized by P501S specific CTL, pools of 18-20 mer or 30-mer peptides that spanned the majority of the amino acid sequence of P501S were loaded onto autologous B-LCL and tested in  $\gamma$ -IFN Elispot assays for the ability to stimulate two P501S-specific CTL clones, referred to as 4E5  
20 and 4E7. One pool, composed of five 18-20 mer peptides that spanned amino acids 411-486 of P501S (SEQ ID NO: 113), was found to be recognized by both P501S-specific clones. To identify the specific 18-20 mer peptide recognized by the clones, each of the 18-20 mer peptides that comprised the positive pool were tested individually in  $\gamma$ -IFN Elispot assays for the ability to stimulate the two P501S-specific CTL clones, 4E5 and  
25 4E7. Both 4E5 and 4E7 specifically recognized one 20-mer peptide (SEQ ID NO: 710; cDNA sequence provided in SEQ ID NO: 711) that spanned amino acids 453-472 of P501S. Since the minimal epitope recognized by CD8+ T cells is almost always either a 9 or 10-mer peptide sequence, 10-mer peptides that spanned the entire sequence of SEQ ID NO: 710 were synthesized that differed by 1 amino acid. Each of these 10-mer  
30 peptides was tested for the ability to stimulate two P501S-specific clones, (referred to as 1D5 and 1E12). One 10-mer peptide (SEQ ID NO: 712; cDNA sequence provided in

SEQ ID NO: 713) was identified that specifically stimulated the P501S-specific clones. This epitope spans amino acids 463-472 of P501S. This sequence defines a minimal 10-mer epitope from P501S that can be naturally processed and to which CTL responses can be identified in normal PBMC. Thus, this epitope is a candidate for use as a vaccine moiety, and as a therapeutic and/or diagnostic reagent for prostate cancer.

To identify the class I restriction element for the P501S-derived sequence of SEQ ID NO: 712, HLA blocking and mismatch analyses were performed. In  $\gamma$ -IFN Elispot assays, the specific response of clones 4A7 and 4E5 to P501S-transduced autologous fibroblasts was blocked by pre-incubation with 25ug/ml W6/32 (pan-Class I blocking antibody) and B1.23.2 (HLA-B/C blocking antibody). These results demonstrate that the SEQ ID NO: 712-specific response is restricted to an HLA-B or HLA-C allele.

For the HLA mismatch analysis, autologous B-LCL (HLA-A1,A2,B8,B51, Cw1, Cw7) and heterologous B-LCL (HLA-A2,A3,B18,B51,Cw5,Cw14) that share the HLAB51 allele were pulsed for one hour with 20ug/ml of peptide of SEQ ID NO: 712, washed, and tested in  $\gamma$ -IFN Elispot assays for the ability to stimulate clones 4A7 and 4E5. Antibody blocking assays with the B1.23.2 (HLA-B/C blocking antibody) were also performed. SEQ ID NO: 712-specific response was detected using both the autologous (D326) and heterologous (D107) B-LCL, and furthermore the responses were blocked by pre-incubation with 25ug/ml of B1.23.2 HLA-B/C blocking antibody. Together these results demonstrate that the P501S-specific response to the peptide of SEQ ID NO: 712 is restricted to the HLA-B51 class I allele. Molecular cloning and sequence analysis of the HLA-B51 allele from D3326 revealed that the HLA-B51 subtype of D326 is HLA-B51011.

Based on the 10-mer P501S-derived epitope of SEQ ID NO: 712, two 9-mers with the sequences of SEQ ID NO: 714 and 715 were synthesized and tested in Elispot assays for the ability to stimulate two P501S-specific CTL clones derived from line 2A2. The 10-mer peptide of SEQ ID NO: 712, as well as the 9-mer peptide of SEQ ID NO: 715, but not the 9-mer peptide of SEQ ID NO: 714, were capable of stimulating the P501S-specific CTL to produce IFN-gamma. These results demonstrate that the peptide of SEQ ID NO: 715 is a 9-mer P501S-derived epitope recognized by P501S-

specific CTL. The DNA sequence encoding the epitope of SEQ ID NO: 715 is provided in SEQ ID NO: 716.

To identify the class I restricting allele for the P501S-derived peptide of SEQ ID NO: 712 and 715 specific response, each of the HLA B and C alleles were  
5 cloned from the donor used in the *in vitro* priming experiment. Sequence analysis indicated that the relevant alleles were HLA-B8, HLA-B51, HLA-Cw01 and HLA-Cw07. Each of these alleles were subcloned into an expression vector and co-transfected together with the P501S gene into VA-13 cells. Transfected VA-13 cells were then tested for the ability to specifically stimulate the P501S-specific CTL in  
10 ELISPOT assays. VA-13 cells transfected with P501S and HLA-B51 were capable of stimulating the P501S-specific CTL to secrete gamma-IFN. VA-13 cells transfected with HLA-B51 alone or P501S + the other HLA-alleles were not capable of stimulating the P501S-specific CTL. These results demonstrate that the restricting allele for the P501S-specific response is the HLAB51 allele. Sequence analysis revealed that the  
15 subtype of the relevant restricting allele is HLA-B51011.

To determine if the P501S-specific CTL could recognize prostate tumor cells that express P501S, the P501S-positive lines LnCAP and CRL2422 (both expressing "moderate" amounts of P501S mRNA and protein), and PC-3 (expressing low amounts of P501S mRNA and protein), plus the P501S-negative cell line DU-145  
20 were retrovirally transduced with the HLA-B51011 allele that was cloned from the donor used to generate the P501S-specific CTL. HLA-B51011- or EGFP-transduced and selected tumor cells were treated with gamma-interferon and androgen (to upregulate stimulatory functions and P501S, respectively) and used in gamma-interferon Elispot assays with the P501S-specific CTL clones 4E5 and 4E7. Untreated  
25 cells were used as a control.

Both 4E5 and 4E7 efficiently and specifically recognized LnCAP and CRL2422 cells that were transduced with the HLA-B51011 allele, but not the same cell lines transduced with EGFP. Additionally, both CTL clones specifically recognized PC-3 cells transduced with HLA-B51011, but not the P501S-negative tumor cell line  
30 DU-145. Treatment with gamma-interferon or androgen did not enhance the ability of CTL to recognize tumor cells. These results demonstrate that P501S-specific CTL,

generated by *in vitro* whole gene priming, specifically and efficiently recognize prostate tumor cell lines that express P501S.

A naturally processed CD4 epitope of P501S was identified as follows.

CD4 cells specific for P501S were prepared as described above. A series  
5 of 16 overlapping peptides were synthesized that spanned approximately 50% of the amino terminal portion of the P501S gene (amino acids 1- 325 of SEQ ID NO: 113). For priming, peptides were combined into pools of 4 peptides, pulsed at 4 µg/ml onto dendritic cells (DC) for 24 hours, with TNF-alpha. DC were then washed and mixed with negatively selected CD4+ T cells in 96 well U-bottom plates. Cultures were re-  
10 stimulated weekly on fresh DC loaded with peptide pools. Following a total of 4 stimulation cycles, cells were rested for an additional week and tested for specificity to APC pulsed with peptide pools using γ-IFN ELISA and proliferation assays. For these assays, adherent monocytes loaded with either the relevant peptide pool at 4µg/ml or an irrelevant peptide at µg/ml were used as APC. T cell lines that demonstrated either  
15 specific cytokine secretion or proliferation were then tested for recognition of individual peptides that were present in the pool. T cell lines could be identified from pools A and B that recognized individual peptides from these pools.

From pool A, lines AD9 and AE10 specifically recognized peptide 1 (SEQ ID NO: 719), and line AF5 recognized peptide 39 (SEQ ID NO: 718). From pool B, line BC6 could be identified that recognized peptide 58 (SEQ ID NO: 717). Each of these lines were stimulated on the specific peptide and tested for specific recognition of the peptide in a titration assay as well as cell lysates generated by infection of HEK 293 cells with adenovirus expressing either P501S or an irrelevant antigen. For these assays, APC-adherent monocytes were pulsed with either 10, 1, or 0.1 µg/ml individual P501S peptides, and DC were pulsed overnight with a 1:5 dilution of adenovirally infected cell lysates. Lines AD9, AE10 and AF5 retained significant recognition of the relevant P501S-derived peptides even at 0.1 mg/ml. Furthermore, line AD9 demonstrated significant (8.1 fold stimulation index) specific activity for lysates from adenovirus-P501S infected cells. These results demonstrate that high affinity CD4 T cell lines can be generated toward P501S-derived epitopes, and that at least a subset of these T cells specific for the P501S derived sequence of SEQ ID NO: 719 are specific for an epitope that is naturally processed by human cells. The DNA sequences encoding the amino acid sequences of SEQ ID NO: 717-719 are provided in SEQ ID NO: 720-722, respectively.

To further characterize the P501S-specific activity of AD9, the line was cloned using anti-CD3. Three clones, referred to as 1A1, 1A9 and 1F5, were identified that were specific for the P501S-1 peptide (SEQ ID NO: 719). To determine the HLA restriction allele for the P501S-specific response, each of these clones was tested in class II antibody blocking and HLA mismatch assays using proliferation and gamma-interferon assays. In antibody blocking assays and measuring gamma-interferon production using ELISA assays, the ability of all three clones to recognize peptide pulsed APC was specifically blocked by co-incubation with either a pan-class II blocking antibody or a HLA-DR blocking antibody, but not with a HLA-DQ or an irrelevant antibody. Proliferation assays performed simultaneously with the same cells confirmed these results. These data indicate that the P501S-specific response of the clones is restricted by an HLA-DR allele. Further studies demonstrated that the restricting allele for the P501S-specific response is HLA-DRB1501.

## EXAMPLE 13

## IDENTIFICATION OF PROSTATE-SPECIFIC ANTIGENS

## BY MICROARRAY ANALYSIS

5           This Example describes the isolation of certain prostate-specific polypeptides from a prostate tumor cDNA library.

          A human prostate tumor cDNA expression library as described above was screened using microarray analysis to identify clones that display at least a three fold over-expression in prostate tumor and/or normal prostate tissue, as compared to  
10 non-prostate normal tissues (not including testis). 372 clones were identified, and 319 were successfully sequenced. Table I presents a summary of these clones, which are shown in SEQ ID NOs:385-400. Of these sequences SEQ ID NOs:386, 389, 390 and 392 correspond to novel genes, and SEQ ID NOs: 393 and 396 correspond to previously identified sequences. The others (SEQ ID NOs:385, 387, 388, 391, 394, 395 and 397-  
15 400) correspond to known sequences, as shown in Table I.

Table I  
Summary of Prostate Tumor Antigens

Known Genes	Previously Identified Genes	Novel Genes
T-cell gamma chain	P504S	23379 (SEQ ID NO:389)
Kallikrein	P1000C	23399 (SEQ ID NO:392)
Vector	P501S	23320 (SEQ ID NO:386)
CGI-82 protein mRNA (23319; SEQ ID NO:385)	P503S	23381 (SEQ ID NO:390)
PSA	P510S	
Ald. 6 Dehyd.	P784P	
L-iditol-2 dehydrogenase (23376; SEQ ID NO:388)	P502S	
Ets transcription factor PDEF (22672; SEQ ID NO:398)	P706P	
hTGR (22678; SEQ ID NO:399)	19142.2, bangur.seq (22621; SEQ ID NO:396)	
KIAA0295(22685; SEQ ID NO:400)	5566.1 Wang (23404; SEQ ID NO:393)	
Prostatic Acid Phosphatase(22655; SEQ ID NO:397)	P712P	
transglutaminase (22611; SEQ ID NO:395)	P778P	
HDLBP (23508; SEQ ID NO:394)		
CGI-69 Protein(23367; SEQ ID NO:387)		
KIAA0122(23383; SEQ ID NO:391)		
TEEG		



CGI-82 showed 4.06 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 43% of prostate tumors, 25% normal prostate, not detected in other normal tissues tested. L-idoitol-2 dehydrogenase showed 4.94 fold over-expression in prostate tissues as compared to  
5 other normal tissues tested. It was over-expressed in 90% of prostate tumors, 100% of normal prostate, and not detected in other normal tissues tested. Ets transcription factor PDEF showed 5.55 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 47% prostate tumors, 25% normal prostate and not detected in other normal tissues tested. hTGR1 showed 9.11 fold over-expression in  
10 prostate tissues as compared to other normal tissues tested. It was over-expressed in 63% of prostate tumors and is not detected in normal tissues tested including normal prostate. KIAA0295 showed 5.59 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 47% of prostate tumors, low to undetectable in normal tissues tested including normal prostate tissues. Prostatic acid  
15 phosphatase showed 9.14 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 67% of prostate tumors, 50% of normal prostate, and not detected in other normal tissues tested. Transglutaminase showed 14.84 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 30% of prostate tumors, 50% of normal prostate, and is  
20 not detected in other normal tissues tested. High density lipoprotein binding protein (HDLBP) showed 28.06 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 97% of prostate tumors, 75% of normal prostate, and is undetectable in all other normal tissues tested. CGI-69 showed 3.56 fold over-expression in prostate tissues as compared to other normal tissues tested. It is  
25 a low abundant gene, detected in more than 90% of prostate tumors, and in 75% normal prostate tissues. The expression of this gene in normal tissues was very low. KIAA0122 showed 4.24 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 57% of prostate tumors, it was undetectable in all normal tissues tested including normal prostate tissues. 19142.2  
30 bangur showed 23.25 fold over-expression in prostate tissues as compared to other

normal tissues tested. It was over-expressed in 97% of prostate tumors and 100% of normal prostate. It was undetectable in other normal tissues tested. .5566.1 Wang showed 3.31 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 97% of prostate tumors, 75% normal prostate and was also over-expressed in normal bone marrow, pancreas, and activated PBMC. Novel clone 23379 (also referred to as P553S) showed 4.86 fold over-expression in prostate tissues as compared to other normal tissues tested. It was detectable in 97% of prostate tumors and 75% normal prostate and is undetectable in all other normal tissues tested. Novel clone 23399 showed 4.09 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 27% of prostate tumors and was undetectable in all normal tissues tested including normal prostate tissues. Novel clone 23320 showed 3.15 fold over-expression in prostate tissues as compared to other normal tissues tested. It was detectable in all prostate tumors and 50% of normal prostate tissues. It was also expressed in normal colon and trachea. Other normal tissues do not express this gene at high level.

Subsequent full-length cloning studies on P553S, using standard techniques, revealed that this clone is an incomplete spliced form of P501S. The determined cDNA sequences for four splice variants of P553S are provided in SEQ ID NO: 623-626. An amino acid sequence encoded by SEQ ID NO: 626 is provided in SEQ ID NO: 627. The cDNA sequence of SEQ ID NO: 623 was found to contain two open reading frames (ORFs). The amino acid sequences encoded by these two ORFs are provided in SEQ ID NO: 628 and 629.

#### EXAMPLE 14

#### IDENTIFICATION OF PROSTATE-SPECIFIC ANTIGENS BY ELECTRONIC SUBTRACTION

This Example describes the use of an electronic subtraction technique to identify prostate-specific antigens.

Potential prostate-specific genes present in the GenBank human EST database were identified by electronic subtraction (similar to that described by Vasmatzis et al., *Proc. Natl. Acad. Sci. USA* 95:300-304, 1998). The sequences of EST clones (43,482) derived from various prostate libraries were obtained from the GenBank public human EST database. Each prostate EST sequence was used as a query sequence in a BLASTN (National Center for Biotechnology Information) search against the human EST database. All matches considered identical (length of matching sequence >100 base pairs, density of identical matches over this region > 70%) were grouped (aligned) together in a cluster. Clusters containing more than 200 ESTs were discarded since they probably represented repetitive elements or highly expressed genes such as those for ribosomal proteins. If two or more clusters shared common ESTs, those clusters were grouped together into a "supercluster," resulting in 4,345 prostate superclusters.

Records for the 479 human cDNA libraries represented in the GenBank release were downloaded to create a database of these cDNA library records. These 479 cDNA libraries were grouped into three groups: Plus (normal prostate and prostate tumor libraries, and breast cell line libraries, in which expression was desired), Minus (libraries from other normal adult tissues, in which expression was not desirable), and Other (libraries from fetal tissue, infant tissue, tissues found only in women, non-prostate tumors and cell lines other than prostate cell lines, in which expression was considered to be irrelevant). A summary of these library groups is presented in Table II.

Table II  
Prostate cDNA Libraries and ESTs

Library	# of Libraries	# of ESTs
Plus	25	43,482
Normal	11	18,875
Tumor	11	21,769
Cell lines	3	2,838
Minus	166	
Other	287	

- 5 Each supercluster was analyzed in terms of the ESTs within the supercluster. The tissue source of each EST clone was noted and used to classify the superclusters into four groups: Type 1- EST clones found in the Plus group libraries only; no expression detected in Minus or Other group libraries; Type 2- EST clones derived from the Plus and Other group libraries only; no expression detected in the
- 10 Minus group; Type 3- EST clones derived from the Plus, Minus and Other group libraries, but the number of ESTs derived from the Plus group is higher than in either the Minus or Other groups; and Type 4- EST clones derived from Plus, Minus and Other group libraries, but the number derived from the Plus group is higher than the number derived from the Minus group. This analysis identified 4,345 breast clusters
- 15 (see Table III). From these clusters, 3,172 EST clones were ordered from Research Genetics, Inc., and were received as frozen glycerol stocks in 96-well plates.

Table III  
Prostate Cluster Summary

Type	# of Superclusters	# of ESTs Ordered
1	688	677
2	2899	2484
3	85	11
4	673	0
Total	4345	3172

5           The EST clone inserts were PCR-amplified using amino-linked PCR primers for Synteni microarray analysis. When more than one PCR product was obtained for a particular clone, that PCR product was not used for expression analysis. In total, 2,528 clones from the electronic subtraction method were analyzed by microarray analysis to identify electronic subtraction breast clones that had high levels  
10 of tumor vs. normal tissue mRNA. Such screens were performed using a Synteni (Palo Alto, CA) microarray, according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA* 93:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA* 94:2150-2155, 1997). Within these analyses, the clones were arrayed on the chip, which was then probed with fluorescent probes  
15 generated from normal and tumor prostate cDNA, as well as various other normal tissues. The slides were scanned and the fluorescence intensity was measured.

          Clones with an expression ratio greater than 3 (*i.e.*, the level in prostate tumor and normal prostate mRNA was at least three times the level in other normal tissue mRNA) were identified as prostate tumor-specific sequences (Table IV). The  
20 sequences of these clones are provided in SEQ ID NO: 401-453, with certain novel sequences shown in SEQ ID NO: 407, 413, 416-419, 422, 426, 427 and 450.

Table IV

Prostate-tumor Specific Clones

SEQ ID NO.	Sequence Designation	Comments
401	22545	previously identified P1000C
402	22547	previously identified P704P
403	22548	known
404	22550	known
405	22551	PSA
406	22552	prostate secretory protein 94
407	22553	novel
408	22558	previously identified P509S
409	22562	glandular kallikrein
410	22565	previously identified P1000C
411	22567	PAP
412	22568	B1006C (breast tumor antigen)
413	22570	novel
414	22571	PSA
415	22572	previously identified P706P
416	22573	novel
417	22574	novel
418	22575	novel
419	22580	novel
420	22581	PAP
421	22582	prostatic secretory protein 94
422	22583	novel
423	22584	prostatic secretory protein 94
424	22585	prostatic secretory protein 94
425	22586	known
426	22587	novel
427	22588	novel
428	22589	PAP
429	22590	known
430	22591	PSA
431	22592	known
432	22593	Previously identified P777P
433	22594	T cell receptor gamma chain
434	22595	Previously identified P705P
435	22596	Previously identified P707P
436	22847	PAP
437	22848	known
438	22849	prostatic secretory protein 57

439	22851	PAP
440	22852	PAP
441	22853	PAP
442	22854	previously identified P509S
443	22855	previously identified P705P
444	22856	previously identified P774P
445	22857	PSA
446	23601	previously identified P777P
447	23602	PSA
448	23605	PSA
449	23606	PSA
450	23612	novel
451	23614	PSA
452	23618	previously identified P1000C
453	23622	previously identified P705P

Further studies on the clone of SEQ ID NO: 407 (also referred to as P1020C) led to the isolation of an extended cDNA sequence provided in SEQ ID NO: 591. This extended cDNA sequence was found to contain an open reading frame that encodes the predicted amino acid sequence of SEQ ID NO: 592. The P1020C cDNA and amino acid sequences were found to show some similarity to the human endogenous retroviral HERV-K pol gene and protein.

#### EXAMPLE 15

##### 10 FURTHER IDENTIFICATION OF PROSTATE-SPECIFIC ANTIGENS BY MICROARRAY ANALYSIS

This Example describes the isolation of additional prostate-specific polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library as described above was screened using microarray analysis to identify clones that display at least a three fold over-expression in prostate tumor and/or normal prostate tissue, as compared to non-prostate normal tissues (not including testis). 142 clones were identified and sequenced. Certain of these clones are shown in SEQ ID NO: 454-467. Of these sequences, SEQ ID NO: 459-460 represent novel genes. The others (SEQ ID NO: 454-458 and 461-467) correspond to known sequences. Comparison of the determined

cDNA sequence of SEQ ID NO: 461 with sequences in the Genbank database using the BLAST program revealed homology to the previously identified transmembrane protease serine 2 (TMPRSS2). The full-length cDNA sequence for this clone is provided in SEQ ID NO: 751, with the corresponding amino acid sequence being  
5 provided in SEQ ID NO: 752. The cDNA sequence encoding the first 209 amino acids of TMPRSS2 is provided in SEQ ID NO: 753, with the first 209 amino acids being provided in SEQ ID NO: 754.

The sequence of SEQ ID NO: 462 (referred to as P835P) was found to correspond to the previously identified clone FLJ13518 (Accession AK023643; SEQ ID  
10 NO: 774), which had no associated open reading frame (ORF). This clone was used to search the Geneseq DNA database and matched a clone previously identified as a G protein-coupled receptor protein (DNA Geneseq Accession A09351; amino acid Geneseq Accession Y92365), that is characterized by the presence of seven transmembrane domains. The sequences of fragments between these domains are  
15 provided in SEQ ID NO: 778-785, with SEQ ID NO: 778, 780, 782 and 784 representing extracellular domains and SEQ ID NO: 779, 781, 783 and 785 representing intracellular domains. SEQ ID NO: 778-785 represent amino acids 1-28, 53-61, 83-103, 124-143, 165-201, 226-238, 263-272 and 297-381, respectively, of P835P. The full-length cDNA sequence for P835P is provided in SEQ ID NO: 773. The cDNA  
20 sequence of the open reading frame for P835P, including stop codon, is provided in SEQ ID NO: 775, with the open reading frame without stop codon being provided in SEQ ID NO: 776 and the corresponding amino acid sequence being provided in SEQ ID NO: 777.

25

#### EXAMPLE 16

##### FURTHER CHARACTERIZATION OF PROSTATE-SPECIFIC ANTIGEN P710P

This Example describes the full length cloning of P710P.

The prostate cDNA library described above was screened with the P710P  
30 fragment described above. One million colonies were plated on LB/Ampicillin plates.



Nylon membrane filters were used to lift these colonies, and the cDNAs picked up by these filters were then denatured and cross-linked to the filters by UV light. The P710P fragment was radiolabeled and used to hybridize with the filters. Positive cDNA clones were selected and their cDNAs recovered and sequenced by an automatic Perkin Elmer/Applied Biosystems Division Sequencer. Four sequences were obtained, and are presented in SEQ ID NO: 468-471. These sequences appear to represent different splice variants of the P710P gene. Subsequent comparison of the cDNA sequences of P710P with those in Genbank revealed homology to the DD3 gene (Genbank accession numbers AF103907 & AF103908). The cDNA sequence of DD3 is provided in SEQ ID NO: 618.

#### EXAMPLE 17

##### PROTEIN EXPRESSION OF PROSTATE-SPECIFIC ANTIGENS

This example describes the expression and purification of prostate-specific antigens in *E. coli*, baculovirus, mammalian and yeast cells.

##### a) Expression of P501S in *E. coli*

Expression of the full-length form of P501S was attempted by first cloning P501S without the leader sequence (amino acids 36-553 of SEQ ID NO: 113) downstream of the first 30 amino acids of the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 484) in pET17b. Specifically, P501S DNA was used to perform PCR using the primers AW025 (SEQ ID NO: 485) and AW003 (SEQ ID NO: 486). AW025 is a sense cloning primer that contains a HindIII site. AW003 is an antisense cloning primer that contains an EcoRI site. DNA amplification was performed using 5 µl 10X Pfu buffer, 1 µl 20 mM dNTPs, 1 µl each of the PCR primers at 10 µM concentration, 40 µl water, 1 µl Pfu DNA polymerase (Stratagene, La Jolla, CA) and 1 µl DNA at 100 ng/µl. Denaturation at 95°C was performed for 30 sec, followed by 10 cycles of 95°C for 30 sec, 60°C for 1 min and by 72°C for 3 min. 20 cycles of 95°C for 30 sec, 65°C for 1 min and by 72°C for 3 min, and lastly by 1 cycle of 72°C for 10 min. The PCR product was

cloned to Ra12m/pET17b using HindIII and EcoRI. The sequence of the resulting fusion construct (referred to as Ra12-P501S-F) was confirmed by DNA sequencing.

The fusion construct was transformed into BL21(DE3)pLysE, pLysS and CodonPlus *E. coli* (Stratagene) and grown overnight in LB broth with kanamycin. The  
5 resulting culture was induced with IPTG. Protein was transferred to PVDF membrane and blocked with 5% non-fat milk (in PBS-Tween buffer), washed three times and incubated with mouse anti-His tag antibody (Clontech) for 1 hour. The membrane was washed 3 times and probed with HRP-Protein A (Zymed) for 30 min. Finally, the membrane was washed 3 times and developed with ECL (Amersham). No expression  
10 was detected by Western blot. Similarly, no expression was detected by Western blot when the Ra12-P501S-F fusion was used for expression in BL21CodonPlus by CE6 phage (Invitrogen).

An N-terminal fragment of P501S (amino acids 36-325 of SEQ ID NO: 113) was cloned down-stream of the first 30 amino acids of the *M. tuberculosis* antigen  
15 Ra12 in pET17b as follows. P501S DNA was used to perform PCR using the primers AW025 (SEQ ID NO: 485) and AW027 (SEQ ID NO: 487). AW027 is an antisense cloning primer that contains an EcoRI site and a stop codon. DNA amplification was performed essentially as described above. The resulting PCR product was cloned to Ra12 in pET17b at the HindIII and EcoRI sites. The fusion construct (referred to as  
20 Ra12-P501S-N) was confirmed by DNA sequencing.

The Ra12-P501S-N fusion construct was used for expression in BL21(DE3)pLysE, pLysS and CodonPlus, essentially as described above. Using Western blot analysis, protein bands were observed at the expected molecular weight of 36 kDa. Some high molecular weight bands were also observed, probably due to  
25 aggregation of the recombinant protein. No expression was detected by Western blot when the Ra12-P501S-F fusion was used for expression in BL21CodonPlus by CE6 phage.

A fusion construct comprising a C-terminal portion of P501S (amino acids 257-553 of SEQ ID NO: 113) located down-stream of the first 30 amino acids of  
30 the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 484) was prepared as follows. P501S

DNA was used to perform PCR using the primers AW026 (SEQ ID NO: 488) and AW003 (SEQ ID NO: 486). AW026 is a sense cloning primer that contains a HindIII site. DNA amplification was performed essentially as described above. The resulting PCR product was cloned to Ra12 in pET17b at the HindIII and EcoRI sites. The  
5 sequence for the fusion construct (referred to as Ra12-P501S-C) was confirmed.

The Ra12-P501S-C fusion construct was used for expression in BL21(DE3)pLysE, pLysS and CodonPlus, as described above. A small amount of protein was detected by Western blot, with some molecular weight aggregates also being observed. Expression was also detected by Western blot when the Ra12-P501S-C  
10 fusion was used for expression in BL21CodonPlus induced by CE6 phage.

A fusion construct comprising a fragment of P501S (amino acids 36-298 of SEQ ID NO: 113) located down-stream of the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 705) was prepared as follows. P501S DNA was used to perform PCR using the primers AW042 (SEQ ID NO: 706) and AW053 (SEQ ID NO: 707). AW042 is a sense  
15 cloning primer that contains a EcoRI site. AW053 is an antisense primer with stop and Xho I sites. DNA amplification was performed essentially as described above. The resulting PCR product was cloned to Ra12 in pET17b at the EcoRI and Xho I sites. The resulting fusion construct (referred to as Ra12-P501S-E2) was expressed in B834 (DE3) pLys S *E. coli* host cells in TB media for 2 h at room temperature. Expressed protein  
20 was purified by washing the inclusion bodies and running on a Ni-NTA column. The purified protein stayed soluble in buffer containing 20 mM Tris-HCl (pH 8), 100 mM NaCl, 10 mM  $\beta$ -Me and 5% glycerol. The determined cDNA and amino acid sequences for the expressed fusion protein are provided in SEQ ID NO: 708 and 709, respectfully.

25 b) Expression of P501S in Baculovirus

The Bac-to-Bac baculovirus expression system (BRL Life Technologies, Inc.) was used to express P501S protein in insect cells. Full-length P501S (SEQ ID NO: 113) was amplified by PCR and cloned into the XbaI site of the donor plasmid pFastBacI. The recombinant bacmid and baculovirus were prepared according to the

manufacturer's instructions. The recombinant baculovirus was amplified in Sf9 cells and the high titer viral stocks were utilized to infect High Five cells (Invitrogen) to make the recombinant protein. The identity of the full-length protein was confirmed by N-terminal sequencing of the recombinant protein and by Western blot analysis (Figure 7). Specifically, 0.6 million High Five cells in 6-well plates were infected with either the unrelated control virus BV/ECD\_PD (lane 2), with recombinant baculovirus for P501S at different amounts or MOIs (lanes 4-8), or were uninfected (lane 3). Cell lysates were run on SDS-PAGE under reducing conditions and analyzed by Western blot with the anti-P501S monoclonal antibody P501S-10E3-G4D3 (prepared as described below). Lane 1 is the biotinylated protein molecular weight marker (BioLabs).

The localization of recombinant P501S in the insect cells was investigated as follows. The insect cells overexpressing P501S were fractionated into fractions of nucleus, mitochondria, membrane and cytosol. Equal amounts of protein from each fraction were analyzed by Western blot with a monoclonal antibody against P501S. Due to the scheme of fractionation, both nucleus and mitochondria fractions contain some plasma membrane components. However, the membrane fraction is basically free from mitochondria and nucleus. P501S was found to be present in all fractions that contain the membrane component, suggesting that P501S may be associated with plasma membrane of the insect cells expressing the recombinant protein.

#### c) Expression of P501S in Mammalian Cells

Full-length P501S (553 amino acids; SEQ ID NO: 113) was cloned into various mammalian expression vectors, including pCEP4 (Invitrogen), pVR1012 (Vical, San Diego, CA) and a modified form of the retroviral vector pBMN, referred to as pBIB. Transfection of P501S/pCEP4 and P501S/pVR1012 into HEK293 fibroblasts was carried out using the Fugene transfection reagent (Boehringer Mannheim). Briefly, 2 ul of Fugene reagent was diluted into 100 ul of serum-free media and incubated at room temperature for 5-10 min. This mixture was added to 1 ug of P501S plasmid DNA, mixed briefly and incubated for 30 minutes at room temperature. The

Fugene/DNA mixture was added to cells and incubated for 24-48 hours. Expression of recombinant P501S in transfected HEK293 fibroblasts was detected by means of Western blot employing a monoclonal antibody to P501S.

Transfection of p501S/pCEP4 into CHO-K cells (American Type Culture Collection, Rockville, MD) was carried out using GenePorter transfection reagent (Gene Therapy Systems, San Diego, CA). Briefly, 15  $\mu$ l of GenePorter was diluted in 500  $\mu$ l of serum-free media and incubated at room temperature for 10 min. The GenePorter/media mixture was added to 2  $\mu$ g of plasmid DNA that was diluted in 500  $\mu$ l of serum-free media, mixed briefly and incubated for 30 min at room temperature. CHO-K cells were rinsed in PBS to remove serum proteins, and the GenePorter/DNA mix was added and incubated for 5 hours. The transfected cells were then fed an equal volume of 2x media and incubated for 24-48 hours.

FACS analysis of P501S transiently infected CHO-K cells, demonstrated surface expression of P501S. Expression was detected using rabbit polyclonal antisera raised against a P501S peptide, as described below. Flow cytometric analysis was performed using a FaCScan (Becton Dickinson), and the data were analyzed using the Cell Quest program.

d) Expression of P501S in *S. cerevisiae*

P501S was expressed in yeast, directed in membranes, using the yeast  $\alpha$  prepro signal sequence. The natural signal sequence and first luminal domain of P501S was deleted in order to conserve the natural positioning of the expressed P501S protein.

Specifically, the  $\alpha$  prepro signal sequence of *S. cerevisiae* linked to amino acids 55-553 of SEQ ID NO: 113 with a His tag tail was cloned into the plasmid pRIT15068 with the CUP1 promoter and transfected into *S. cerevisiae* strain Y1790. The Y1790 strain is Leu<sup>+</sup> and His<sup>-</sup>. Expression of protein was induced by addition of either 500  $\mu$ M or 250  $\mu$ M of CuSO<sub>4</sub> at 30 °C in minimal medium supplemented with histidine. Cells were harvested 24 hours after induction. Extracts were prepared by growing cells to a concentration of OD<sub>600</sub> 5.0 in 50 mM citrate phosphate buffer (pH 4.0) plus 130 mM NaCl supplemented with protease inhibitors. Cells were disrupted

using glass beads and centrifuged for 20 min at 15,000 g. The recombinant protein was found to be 100% pellet associated.

Expression of the recombinant protein (molecular weight 63 kD) was demonstrated by Western blot analysis, using the anti-P501S monoclonal antibody 10E-D4-G3 described below. The amino acid sequence of the expressed protein is provided in SEQ ID NO: 792.

Fermentation processes for the production of the  $\alpha$  prepro-P501S-His tag recombinant protein in *S. cerevisiae* (strain Y1790 – CUP1 inducible promoter) were evaluated as follows. One hundred  $\mu$ l of a master seed containing  $2.5 \times 10^8$  cells/ml of transformed *S. cerevisiae* Y1790 were spread on FSC004AA solid medium. The composition of the FSC004AA medium is as follows: glucose 10 g/l;  $\text{Na}_2\text{MoO}_4 \cdot 2\text{H}_2\text{O}$  0.0002 g/l; folic acid 0.000064 g/l;  $\text{KH}_2\text{PO}_4$  1 g/l;  $\text{MnSO}_4 \cdot \text{H}_2\text{O}$  0.0004 g/l; Inositol 0.064 g/l;  $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$  0.5 g/l;  $\text{H}_3\text{BO}_3$  0.0005 g/l; Pyridoxine 0.008 g/l;  $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$  0.1 g/l; KI 0.0001 g/l; Thiamine 0.008 g/l; NaCl 0.1 g/l;  $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$  0.00009 g/l; Niacin 0.000032 g/l;  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  0.0002 g/l; Riboflavin 0.000016 g/l; Panthotenate Ca 0.008 g/l;  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  0.00004 g/l; Biotin 0.000064 g/l; para-aminobenzoic acid 0.000016 g/l;  $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$  0.0004 g/l;  $(\text{NH}_4)_2\text{SO}_4$  5 g/l; agar 18 g/l; Histidine 0.1 g/l.

Two plates were incubated for 26 h at 30 °C. These solid pre-cultures were harvested in 5 ml of liquid medium FSC007AA and 0.5 ml (or  $9.3 \times 10^7$  cells) of this suspension was used to inoculate 2 liquid pre-cultures.

The composition of the FSC007AA medium is as follows: Glucose 10 g/l;  $\text{Na}_2\text{MoO}_4 \cdot 2\text{H}_2\text{O}$  0.0002 g/l; folic acid 0.000064 g/l;  $\text{KH}_2\text{PO}_4$  1 g/l;  $\text{MnSO}_4 \cdot \text{H}_2\text{O}$  0.0004 g/l; Inositol 0.064 g/l;  $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$  0.5 g/l;  $\text{H}_3\text{BO}_3$  0.0005 g/l; Pyridoxine 0.008 g/l;  $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$  0.1 g/l; KI 0.0001 g/l; Thiamine 0.008 g/l; NaCl 0.1 g/l;  $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$  0.00009 g/l; Niacine 0.000032 g/l;  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  0.0002 g/l; Riboflavin 0.000016 g/l; Panthotenate Ca 0.008 g/l;  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  0.00004 g/l; Biotin 0.000064 g/l; para-aminobenzoic acid 0.000016 g/l;  $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$  0.0004 g/l;  $(\text{NH}_4)_2\text{SO}_4$  5 g/l; Histidine 0.1 g/l.

These pre-cultures were run for 20 hours in 2L flasks containing 400 ml of medium FSC007AA in order to obtain an OD of 1.8. The other characteristics of these pre-cultures are as follows: pH 2.8; glucose 2.3 g/L; ethanol 3.4 g/L.

The best timing for liquid pre-cultures for strain Y1790 was determined in preliminary experiments. Liquid pre-cultures containing 400 ml of medium and inoculated with various volumes of Master Seed (0.25, 0.5, 1 or 2 ml) were monitored in order to identify the best inoculum size and timing. Glucose, ethanol, pH, OD and  
 5 cell number (determined by flow cytometry) were followed between 16 and 23 hours of culture. Glucose exhaustion and maximal biomass were obtained after 20 hour incubation with 0.5 inoculum. These conditions were adopted for transferring the pre-culture into fermentation.

In total, 800ml of pre-culture were used to inoculate a 20 L fermenter  
 10 containing 5L of medium FSC002AA. Three ml of irradiated antifoam were added before inoculation. The composition of the FSC002AA medium is as follows:  
 (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub> 6.4 g/l; Na<sub>2</sub>MoO<sub>4</sub>·2H<sub>2</sub>O 2.05 mg/l; folic acid 0.54 mg/l; KH<sub>2</sub>PO<sub>4</sub> 8.25 g/l;  
 MnSO<sub>4</sub>·H<sub>2</sub>O 4.1 mg/l; inositol 540 mg/l; MgSO<sub>4</sub>·7H<sub>2</sub>O 4.69 g/l; H<sub>3</sub>BO<sub>3</sub> 5.17 mg/l;  
 pyridoxine 68 mg/l; CaCl<sub>2</sub>·2H<sub>2</sub>O 0.92 g/l; KI 1.03 mg/l; thiamine 68 mg/l; NaCl 0.06g/l;  
 15 CoCl<sub>2</sub>·6H<sub>2</sub>O 0.92 mg/l; Niacine 0.27 mg/l; HCl 1 ml/l; FeCl<sub>3</sub>·6H<sub>2</sub>O 9.92 mg/l;  
 Riboflavin 0.13 mg/l; CuSO<sub>4</sub>·5H<sub>2</sub>O 0.41 mg/l; Glucose 0.14 g/l; Panthotenate Ca 68  
 mg/l; ZnSO<sub>4</sub>·7H<sub>2</sub>O 4.1 mg/l; Biotin 0.54 mg/l; para-aminobenzoic acid 0.13 mg/l;  
 Histidine 0.3 g/l

The carbon source (glucose) was supplemented by a continuous feeding  
 20 of FFB004AA medium. The composition of the FFB004AA medium is as follows:  
 glucose 350 g/l; Na<sub>2</sub>MoO<sub>4</sub>·2H<sub>2</sub>O 5.15 mg/l; folic acid 1.36 mg/l; KH<sub>2</sub>PO<sub>4</sub> 20.6 g/l;  
 MnSO<sub>4</sub>·H<sub>2</sub>O 10.3 mg/l; inositol 1350 mg/l; MgSO<sub>4</sub>·7H<sub>2</sub>O 11.7 g/l; H<sub>3</sub>BO<sub>3</sub> 12.9 mg/l;  
 pyridoxine 170 mg/l; CaCl<sub>2</sub>·2H<sub>2</sub>O 2.35 g/l; KI 2.6 mg/l; thiamine 170 g/l; NaCl 0.15 g/l;  
 CoCl<sub>2</sub>·6H<sub>2</sub>O 2.3 mg/l; niacine 0.67 mg/l; HCl 2.5 ml/l; FeCl<sub>3</sub>·6H<sub>2</sub>O 24.8 mg/l;  
 25 riboflavin; 0.33 mg/l; CuSO<sub>4</sub>·5H<sub>2</sub>O 1.03 mg/l; biotin 1.36 mg/l; panthotenate Ca 170  
 mg/l; ZnSO<sub>4</sub>·7H<sub>2</sub>O 10.3 mg/l; para-aminobenzoic acid: 0.33 mg/l; histidine 5.35 g/l.

The residual glucose concentration was maintained very low (□50 mg/L) in order to minimize ethanol production by fermentation. This was achieved by limiting the development of the microorganism using a limited glucose feed rate. The Standard  
 30 biomass content (OD 80-90) was reached in fermentation after 44 hour growth phase.

CUP1 promoter was then induced by adding 500μM CuSO<sub>4</sub> in order to

produce P501S antigen.  $\text{CuSO}_4$  addition was followed by ethanol accumulation (up to 6 g/L), and the glucose feeding rate was then reduced in order to consume the ethanol. The copper available for the microorganism was monitored by testing Cu ion concentration in the broth supernatant using a spectrophotometric copper assay (DETC method). The fermentation was then supplemented by  $\text{CuSO}_4$  throughout the induction phase in order to maintain its concentration between 150 and 250  $\mu\text{M}$  in the supernatant. The biomass reached an OD of 100 at the end of induction. Cells were harvested after 8 hours of induction.

Cell homogenate was prepared and analysed by SDS-PAGE and Western Blot using standard protocols. A major protein band with the expected molecular weight of 62KD was detected by Western blot using anti-P501S monoclonal antibodies. Western blot analysis also showed that the major 62KD band was progressively produced from 30 minutes of induction on, and reached a maximum after 3 hours. No more antigen seemed to be produced between 3 and 12 hours of induction.

The number of passages through a French Press necessary to extract all the antigen from the cells was evaluated. One, three and five passages were tested and total cell lysates, supernatants and pellets of cell lysates were analysed by Western blot. Three passages through a French Press were sufficient to completely extract the antigen. The antigen was present in the insoluble fraction.

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#### e) Expression of P703P in Baculovirus

The cDNA for full-length P703P-DE5 (SEQ ID NO: 326), together with several flanking restriction sites, was obtained by digesting the plasmid pCDNA703 with restriction endonucleases Xba I and Hind III. The resulting restriction fragment (approx. 800 base pairs) was ligated into the transfer plasmid pFastBacI which was digested with the same restriction enzymes. The sequence of the insert was confirmed by DNA sequencing. The recombinant transfer plasmid pFBP703 was used to make recombinant bacmid DNA and baculovirus using the Bac-To-Bac Baculovirus expression system (BRL Life Technologies). High Five cells were infected with the recombinant virus BVP703, as described above, to obtain recombinant P703P protein.

30



e) Expression of P788P in *E. Coli*

A truncated, N-terminal portion, of P788P (residues 1-644 of SEQ ID NO: 777; referred to as P788P-N) fused with a C-terminal 6xHis Tag was expressed in *E. coli* as follows. P788P cDNA was amplified using the primers AW080 and AW081 (SEQ ID NO: 672 and 673). AW080 is a sense cloning primer with an NdeI site. AW081 is an antisense cloning primer with a XhoI site. The PCR-amplified P788P, as well as the vector pCRX1, were digested with NdeI and XhoI. Vector and insert were ligated and transformed into NovaBlue cells. Colonies were randomly screened for insert and then sequenced. P788P-N clone #6 was confirmed to be identical to the designed construct. The expression construct P788P-N #6/pCRX1 was transformed into *E. coli* BL21 CodonPlus-RIL competent cells. After induction, most of the cells grew well, achieving OD600 of greater than 2.0 after 3 hr. Coomassie stained SDS-PAGE showed an over-expressed band at about 75 kD. Western blot analysis using a 6xHisTag antibody confirmed the band was P788P-N. The determined cDNA sequence for P788P-N is provided in SEQ ID NO: 674, with the corresponding amino acid sequence being provided in SEQ ID NO: 675.

f) Expression of P510S in *E. Coli*

The P510S protein has 9 potential transmembrane domains and is predicted to be located at the plasma membrane. The C-terminal protein of this protein, as well as the predicted third extracellular domain of P510S were expressed in *E. coli* as follows.

The expression construct referred to as Ra12-P501S-C was designed to have a 6 HisTag at the N-terminal end, followed by the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 676) and then the C-terminal portion of P510S (amino residues 1176-1261 of SEQ ID NO: 538). Full-length P510S was used to amplify the P510S-C fragment by PCR using the primers AW056 and AW057 (SEQ ID NO: 677 and 678, respectively). AW056 is a sense cloning primer with an EcoRI site. AW057 is an antisense primer with stop and XhoI sites. The amplified P501S fragment and Ra12/pCRX1 were digested with EcoRI and XhoI and then purified. The insert and

vector were ligated together and transformed into NovaBlue. Colonies were randomly screened for insert and sequences. For protein expression, the expression construct was transformed into *E. coli* BL21 (DE3) CodonPlus-RIL competent cells. A mini-induction screen was performed to optimize the expression conditions. After induction  
5 the cells grew well, achieving OD 600 nm greater than 2.0 after 3 hours. Coomassie stain SDS-PAGE showed a highly over-expressed band at approx. 30 kD. Though this is higher than the expected molecular weight, western blot analysis was positive, showing this band to be the His tag-containing protein. The optimized culture conditions are as follows. Dilute overnight culture/daytime culture (LB + kanamycin +  
10 chloramphenicol) into 2xYT (with kanamycin and chloramphenicol) at a ratio of 25 ml culture to 1 liter 2xYT. Allow to grow at 37 °C until OD600 = 0.6. Take an aliquot out as T0 sample. Add 1 mM IPTG and allow to grow at 30 °C for 3 hours. Take out a T3 sample, spin down cells and store at -80 °C. The determined cDNA and amino acid sequences for the Ra12-P510S-C construct are provided in SEQ ID NO: 679 and 682,  
15 respectively.

The expression construct P510S-C was designed to have a 5' added start codon and a glycine (GGA) codon and then the P510S C terminal fragment followed by the in frame 6x histidine tag and stop codon from the pET28b vector. The cloning strategy is similar to that used for Ra12-P510S-C, except that the PCR primers employed were  
20 those shown in SEQ ID NO: 685 and 686, respectively and the NcoI/XhoI cut in pET28b was used. The primer of SEQ ID NO: 685 created a 5' NcoI site and added a start codon. The antisense primer of SEQ ID NO: 686 creates a XhoI site on P510S C terminal fragment. Clones were confirmed by sequencing. For protein expression, the expression construct was transformed into *E. coli* BL21 (DE3) CodonPlus-RIL  
25 competent cells. An OD600 of greater than 2.0 was obtained 30 hours after induction. Coomassie stained SDS-PAGE showed an over-expressed band at about 11 kD. Western blot analysis confirmed that the band was P510S-C, as did N-terminal protein sequencing. The optimized culture conditions are as follows: dilute overnight culture/daytime culture (LB + kanamycin + chloramphenicol) into 2x YT (+ kanamycin  
30 and chloramphenicol) at a ratio of 25 mL culture to 1 liter 2x YT, and allow to grow at

37 °C until an OD 600 of about 0.5 is reached. Take out an aliquot as T0 sample. Add 1 mM IPTG and allow to grow at 30 °C for 3 hours. Spin down the cells and store at -80 °C until purification. The determined cDNA and amino acid sequences for the P510S-C construct are shown in SEQ ID NO: 680 and 683, respectively.

- 5                   The predicted third extracellular domain of P510S (P510S-E3; residues 328-676 of SEQ ID NO: 538) was expressed in *E. coli* as follows. The P510S fragment was amplified by PCR using the primers shown in SEQ ID NO: 687 and 688. The primer of SEQ ID NO: 687 is a sense primer with an NdeI site for use in ligating into pPDM. The primer of SEQ ID NO: 688 is an antisense primer with an added XhoI site  
10 for use in ligating into pPDM. The resulting fragment was cloned to pPDM at the NdeI and XhoI sites. Clones were confirmed by sequencing. For protein expression, the clone was transformed into *E. coli* BL21 (DE3) CodonPlus-RIL competent cells. After induction, an OD600 of greater than 2.0 was achieved after 3 hours. Coomassie stained SDS-PAGE showed an over-expressed band at about 39 kD, and N-terminal sequencing  
15 confirmed the N-terminal to be that of P510S-E3. Optimized culture conditions are as follows: dilute overnight culture/daytime culture (LB + kanamycin + chloramphenicol) into 2x YT (kanamycin and chloramphenicol) at a ratio of 25 ml culture to 1 liter 2x YT. Allow to grow at 37 °C until OD 600 equals 0.6. Take out an aliquot as T0 sample. Add 1 mM IPTG and allow to grow at 30 °C for 3 hours. Take out a T3  
20 sample, spin down the cells and store at -80 °C until purification. The determined cDNA and amino acid sequences for the P501S-E3 construct are provided in SEQ ID NO: 681 and 684, respectively.

g) Expression of P775S in *E. Coli*

- The antigen P775P contains multiple open reading frames (ORF). The  
25 third ORF, encoding the protein of SEQ ID NO: 483, has the best motif score. An expression fusion construct containing the *M. tuberculosis* antigen Ra12 (SEQ ID NO: 676) and P775P-ORF3 with an N-terminal 6x HisTag was prepared as follows. P775P-ORF3 was amplified using the sense PCR primers of SEQ ID NO: 689 and the anti-sense PCR primer of SEQ ID NO: 690. The PCR amplified fragment of P775P and

Ra12/pCRX1 were digested with the restriction enzymes EcoRI and XhoI. Vector and insert were ligated and then transformed into NovaBlue cells. Colonies were randomly screened for insert and then sequenced. A clone having the desired sequence was transformed into *E. coli* BL21 (DE3) CodonPlus-RIL competent cells. Two hours after  
5 induction, the cell density peaked at OD600 of approximately 1.8. Coomassie stained SDS-PAGE showed an over-expressed band at about 31 kD. Western blot using 6x HisTag antibody confirmed that the band was Ra12-P775P-ORF3. The determined cDNA and amino acid sequences for the fusion construct are provided in SEQ ID NO: 691 and 692, respectively.

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#### H) EXPRESSION OF A P703P HIS TAG FUSION PROTEIN IN *E. COLI*

The cDNA for the coding region of P703P was prepared by PCR using the primers of SEQ ID NO: 693 and 694. The PCR product was digested with EcoRI restriction enzyme, gel purified and cloned into a modified pET28 vector with a His tag  
15 in frame, which had been digested with Eco72I and EcoRI restriction enzymes. The correct construct was confirmed by DNA sequence analysis and then transformed into *E. coli* BL21 (DE3) pLys S expression host cells. The determined amino acid and cDNA sequences for the expressed recombinant P703P are provided in SEQ ID NO: 695 and 696, respectively.

20

#### I) EXPRESSION OF A P705P HIS TAG FUSION PROTEIN IN *E. COLI*

The cDNA for the coding region of P705P was prepared by PCR using the primers of SEQ ID NO: 697 and 698. The PCR product was digested with EcoRI restriction enzyme, gel purified and cloned into a modified pET28 vector with a His tag  
25 in frame, which had been digested with Eco72I and EcoRI restriction enzymes. The correct construct was confirmed by DNA sequence analysis and then transformed into *E. coli* BL21 (DE3) pLys S and BL21 (DE3) CodonPlus expression host cells. The determined amino acid and cDNA sequences for the expressed recombinant P705P are provided in SEQ ID NO: 699 and 700, respectively.

30

#### J) EXPRESSION OF A P711P HIS TAG FUSION PROTEIN IN *E. COLI*

The cDNA for the coding region of P711P was prepared by PCR using the primers of SEQ ID NO: 701 and 702. The PCR product was digested with EcoRI restriction enzyme, gel purified and cloned into a modified pET28 vector with a His tag in frame, which had been digested with Eco72I and EcoRI restriction enzymes. The correct construct was confirmed by DNA sequence analysis and then transformed into *E. coli* BL21 (DE3) pLys S and BL21 (DE3) CodonPlus expression host cells. The determined amino acid and cDNA sequences for the expressed recombinant P711P are provided in SEQ ID NO: 703 and 704, respectively.

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#### EXAMPLE 18

##### PREPARATION AND CHARACTERIZATION OF ANTIBODIES AGAINST PROSTATE-SPECIFIC POLYPEPTIDES

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##### a) Preparation and Characterization of Polyclonal Antibodies against P703P, P504S and P509S

Polyclonal antibodies against P703P, P504S and P509S were prepared as follows.

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Each prostate tumor antigen expressed in an *E. coli* recombinant expression system was grown overnight in LB broth with the appropriate antibiotics at 37°C in a shaking incubator. The next morning, 10 ml of the overnight culture was added to 500 ml to 2x YT plus appropriate antibiotics in a 2L-baffled Erlenmeyer flask. When the Optical Density (at 560 nm) of the culture reached 0.4-0.6, the cells were induced with IPTG (1 mM). Four hours after induction with IPTG, the cells were harvested by centrifugation. The cells were then washed with phosphate buffered saline and centrifuged again. The supernatant was discarded and the cells were either frozen for future use or immediately processed. Twenty ml of lysis buffer was added to the cell pellets and vortexed. To break open the *E. coli* cells, this mixture was then run

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through the French Press at a pressure of 16,000 psi. The cells were then centrifuged again and the supernatant and pellet were checked by SDS-PAGE for the partitioning of the recombinant protein. For proteins that localized to the cell pellet, the pellet was resuspended in 10 mM Tris pH 8.0, 1% CHAPS and the inclusion body pellet was washed and centrifuged again. This procedure was repeated twice more. The washed inclusion body pellet was solubilized with either 8 M urea or 6 M guanidine HCl containing 10 mM Tris pH 8.0 plus 10 mM imidazole. The solubilized protein was added to 5 ml of nickel-chelate resin (Qiagen) and incubated for 45 min to 1 hour at room temperature with continuous agitation. After incubation, the resin and protein mixture were poured through a disposable column and the flow through was collected. The column was then washed with 10-20 column volumes of the solubilization buffer. The antigen was then eluted from the column using 8M urea, 10 mM Tris pH 8.0 and 300 mM imidazole and collected in 3 ml fractions. A SDS-PAGE gel was run to determine which fractions to pool for further purification.

As a final purification step, a strong anion exchange resin such as HiPrepQ (Biorad) was equilibrated with the appropriate buffer and the pooled fractions from above were loaded onto the column. Each antigen was eluted off the column with a increasing salt gradient. Fractions were collected as the column was run and another SDS-PAGE gel was run to determine which fractions from the column to pool. The pooled fractions were dialyzed against 10 mM Tris pH 8.0. The proteins were then vialled after filtration through a 0.22 micron filter and the antigens were frozen until needed for immunization.

Four hundred micrograms of each prostate antigen was combined with 100 micrograms of muramyl dipeptide (MDP). Every four weeks rabbits were boosted with 100 micrograms mixed with an equal volume of Incomplete Freund's Adjuvant (IFA). Seven days following each boost, the animal was bled. Sera was generated by incubating the blood at 4°C for 12-4 hours followed by centrifugation.

Ninety-six well plates were coated with antigen by incubating with 50 microliters (typically 1 microgram) of recombinant protein at 4 °C for 20 hours. 250 microliters of BSA blocking buffer was added to the wells and incubated at room

temperature for 2 hours. Plates were washed 6 times with PBS/0.01% Tween. Rabbit sera was diluted in PBS. Fifty microliters of diluted sera was added to each well and incubated at room temperature for 30 min. Plates were washed as described above before 50 microliters of goat anti-rabbit horse radish peroxidase (HRP) at a 1:10000 dilution was added and incubated at room temperature for 30 min. Plates were again washed as described above and 100 microliters of TMB microwell peroxidase substrate was added to each well. Following a 15 min incubation in the dark at room temperature, the colorimetric reaction was stopped with 100 microliters of 1N H<sub>2</sub>SO<sub>4</sub> and read immediately at 450 nm. All polyclonal antibodies showed immunoreactivity to the appropriate antigen.

b) Preparation and Characterization of Antibodies against P501S

A murine monoclonal antibody directed against the carboxy-terminus of the prostate-specific antigen P501S was prepared as follows.

A truncated fragment of P501S (amino acids 355-526 of SEQ ID NO: 113) was generated and cloned into the pET28b vector (Novagen) and expressed in *E. coli* as a thioredoxin fusion protein with a histidine tag. The trx-P501S fusion protein was purified by nickel chromatography, digested with thrombin to remove the trx fragment and further purified by an acid precipitation procedure followed by reverse phase HPLC.

Mice were immunized with truncated P501S protein. Serum bleeds from mice that potentially contained anti-P501S polyclonal sera were tested for P501S-specific reactivity using ELISA assays with purified P501S and trx-P501S proteins. Serum bleeds that appeared to react specifically with P501S were then screened for P501S reactivity by Western analysis. Mice that contained a P501S-specific antibody component were sacrificed and spleen cells were used to generate anti-P501S antibody producing hybridomas using standard techniques. Hybridoma supernatants were tested for P501S-specific reactivity initially by ELISA, and subsequently by FACS analysis of reactivity with P501S transduced cells. Based on these results, a monoclonal hybridoma referred to as 10E3 was chosen for further subcloning. A number of subclones were

generated, tested for specific reactivity to P501S using ELISA and typed for IgG isotype. The results of this analysis are shown below in Table V. Of the 16 subclones tested, the monoclonal antibody 10E3-G4-D3 was selected for further study.

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Table V

Isotype analysis of murine anti-P501S monoclonal antibodies

Hybridoma clone	Isotype	Estimated [Ig] in supernatant ( $\mu\text{g/ml}$ )
4D11	IgG1	14.6
1G1	IgG1	0.6
4F6	IgG1	72
4H5	IgG1	13.8
4H5-E12	IgG1	10.7
4H5-EH2	IgG1	9.2
4H5-H2-A10	IgG1	10
4H5-H2-A3	IgG1	12.8
4H5-H2-A10-G6	IgG1	13.6
4H5-H2-B11	IgG1	12.3
10E3	IgG2a	3.4
10E3-D4	IgG2a	3.8
10E3-D4-G3	IgG2a	9.5
10E3-D4-G6	IgG2a	10.4
10E3-E7	IgG2a	6.5
8H12	IgG2a	0.6

The specificity of 10E3-G4-D3 for P501S was examined by FACS analysis. Specifically, cells were fixed (2% formaldehyde, 10 minutes), permeabilized (0.1% saponin, 10 minutes) and stained with 10E3-G4-D3 at 0.5 – 1  $\mu\text{g/ml}$ , followed by incubation with a secondary, FITC-conjugated goat anti-mouse Ig antibody (Pharmingen, San Diego, CA). Cells were then analyzed for FITC fluorescence using an Excalibur fluorescence activated cell sorter. For FACS analysis of transduced cells, B-LCL were retrovirally transduced with P501S. For analysis of infected cells, B-LCL were infected with a vaccinia vector that expresses P501S. To demonstrate specificity in these assays, B-LCL transduced with a different antigen (P703P) and uninfected B-LCL vectors were utilized. 10E3-G4-D3 was shown to bind with P501S-transduced B-

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LCL and also with P501S-infected B-LCL, but not with either uninfected cells or P703P-transduced cells.

To determine whether the epitope recognized by 10E3-G4-D3 was found on the surface or in an intracellular compartment of cells, B-LCL were transduced with  
5 P501S or HLA-B8' as a control antigen and either fixed and permeabilized as described above or directly stained with 10E3-G4-D3 and analyzed as above. Specific recognition of P501S by 10E3-G4-D3 was found to require permeabilization, suggesting that the epitope recognized by this antibody is intracellular.

The reactivity of 10E3-G4-D3 with the three prostate tumor cell lines  
10 Lncap, PC-3 and DU-145, which are known to express high, medium and very low levels of P501S, respectively, was examined by permeabilizing the cells and treating them as described above. Higher reactivity of 10E3-G4-D3 was seen with Lncap than with PC-3, which in turn showed higher reactivity than DU-145. These results are in agreement with the real time PCR and demonstrate that the antibody specifically  
15 recognizes P501S in these tumor cell lines and that the epitope recognized in prostate tumor cell lines is also intracellular.

Specificity of 10E3-G4-D3 for P501S was also demonstrated by Western blot analysis. Lysates from the prostate tumor cell lines Lncap, DU-145 and PC-3, from P501S-transiently transfected HEK293 cells, and from non-transfected HEK293 cells  
20 were generated. Western blot analysis of these lysates with 10E3-G4-D3 revealed a 46 kDa immunoreactive band in Lncap, PC-3 and P501S-transfected HEK cells, but not in DU-145 cells or non-transfected HEK293 cells. P501S mRNA expression is consistent with these results since semi-quantitative PCR analysis revealed that P501S mRNA is expressed in Lncap, to a lesser but detectable level in PC-3 and not at all in DU-145  
25 cells. Bacterially expressed and purified recombinant P501S (referred to as P501SStr2) was recognized by 10E3-G4-D3 (24 kDa), as was full-length P501S that was transiently expressed in HEK293 cells using either the expression vector VR1012 or pCEP4. Although the predicted molecular weight of P501S is 60.5 kDa, both transfected and "native" P501S run at a slightly lower mobility due to its hydrophobic nature.

Immunohistochemical analysis was performed on prostate tumor and a panel of normal tissue sections (prostate, adrenal, breast, cervix, colon, duodenum, gall bladder, ileum, kidney, ovary, pancreas, parotid gland, skeletal muscle, spleen and testis). Tissue samples were fixed in formalin solution for 24 hours and embedded in paraffin before being sliced into 10 micron sections. Tissue sections were permeabilized and incubated with 10E3-G4-D3 antibody for 1 hr. HRP-labeled anti-mouse followed by incubation with DAB chromogen was used to visualize P501S immunoreactivity. P501S was found to be highly expressed in both normal prostate and prostate tumor tissue but was not detected in any of the other tissues tested.

To identify the epitope recognized by 10E3-G4-D3, an epitope mapping approach was pursued. A series of 13 overlapping 20-21 mers (5 amino acid overlap; SEQ ID NO: 489-501) was synthesized that spanned the fragment of P501S used to generate 10E3-G4-D3. Flat bottom 96 well microtiter plates were coated with either the peptides or the P501S fragment used to immunize mice, at 1 microgram/ml for 2 hours at 37 °C. Wells were then aspirated and blocked with phosphate buffered saline containing 1% (w/v) BSA for 2 hours at room temperature, and subsequently washed in PBS containing 0.1% Tween 20 (PBST). Purified antibody 10E3-G4-D3 was added at 2 fold dilutions (1000 ng – 16 ng) in PBST and incubated for 30 minutes at room temperature. This was followed by washing 6 times with PBST and subsequently incubating with HRP-conjugated donkey anti-mouse IgG (H+L)Affinipure F(ab') fragment (Jackson ImmunoResearch, West Grove, PA) at 1:20000 for 30 minutes. Plates were then washed and incubated for 15 minutes in tetramethyl benzidine. Reactions were stopped by the addition of 1N sulfuric acid and plates were read at 450 nm using an ELISA plate reader. As shown in Fig. 8, reactivity was seen with the peptide of SEQ ID NO: 496 (corresponding to amino acids 439-459 of P501S) and with the P501S fragment but not with the remaining peptides, demonstrating that the epitope recognized by 10E3-G4-D3 is localized to amino acids 439-459 of SEQ ID NO: 113.

In order to further evaluate the tissue specificity of P501S, multi-array immunohistochemical analysis was performed on approximately 4700 different human tissues encompassing all the major normal organs as well as neoplasias derived from

these tissues. Sixty-five of these human tissue samples were of prostate origin. Tissue sections 0.6 mm in diameter were formalin-fixed and paraffin embedded. Samples were pretreated with HIER using 10 mM citrate buffer pH 6.0 and boiling for 10 min. Sections were stained with 10E3-G4-D3 and P501S immunoreactivity was visualized with HRP. All the 65 prostate tissues samples (5 normal, 55 untreated prostate tumors, 5 hormone refractory prostate tumors) were positive, showing distinct perinuclear staining. All other tissues examined were negative for P501S expression.

c) Preparation and Characterization of Antibodies against P503S

A fragment of P503S (amino acids 113-241 of SEQ ID NO: 114) was expressed and purified from bacteria essentially as described above for P501S and used to immunize both rabbits and mice. Mouse monoclonal antibodies were isolated using standard hybridoma technology as described above. Rabbit monoclonal antibodies were isolated using Selected Lymphocyte Antibody Method (SLAM) technology at Immgenics Pharmaceuticals (Vancouver, BC, Canada). Table VI, below, lists the monoclonal antibodies that were developed against P503S.

Table VI

Antibody	Species
20D4	Rabbit
JA1	Rabbit
1A4	Mouse
1C3	Mouse
1C9	Mouse
1D12	Mouse
2A11	Mouse
2H9	Mouse
4H7	Mouse
8A8	Mouse
8D10	Mouse
9C12	Mouse
6D12	Mouse

The DNA sequences encoding the complementarity determining regions (CDRs) for the rabbit monoclonal antibodies 20D4 and JA1 were determined and are provided in SEQ ID NO: 502 and 503, respectively.

5 In order to better define the epitope binding region of each of the antibodies, a series of overlapping peptides were generated that span amino acids 109-213 of SEQ ID NO: 114. These peptides were used to epitope map the anti-P503S monoclonal antibodies by ELISA as follows. The recombinant fragment of P503S that was employed as the immunogen was used as a positive control. Ninety-six well  
10 microtiter plates were coated with either peptide or recombinant antigen at 20 ng/well overnight at 4 °C. Plates were aspirated and blocked with phosphate buffered saline containing 1% (w/v) BSA for 2 hours at room temperature then washed in PBS containing 0.1% Tween 20 (PBST). Purified rabbit monoclonal antibodies diluted in PBST were added to the wells and incubated for 30 min at room temperature. This was  
15 followed by washing 6 times with PBST and incubation with Protein-A HRP conjugate at a 1:2000 dilution for a further 30 min. Plates were washed six times in PBST and incubated with tetramethylbenzidine (TMB) substrate for a further 15 min. The reaction was stopped by the addition of 1N sulfuric acid and plates were read at 450 nm using at ELISA plate reader. ELISA with the mouse monoclonal antibodies was performed with  
20 supernatants from tissue culture run neat in the assay.

All of the antibodies bound to the recombinant P503S fragment, with the exception of the negative control SP2 supernatant. 20D4, JA1 and 1D12 bound strictly to peptide #2101 (SEQ ID NO: 504), which corresponds to amino acids 151-169 of SEQ ID NO: 114. 1C3 bound to peptide #2102 (SEQ ID NO: 505), which corresponds  
25 to amino acids 165-184 of SEQ ID NO: 114. 9C12 bound to peptide #2099 (SEQ ID NO: 522), which corresponds to amino acids 120-139 of SEQ ID NO: 114. The other antibodies bind to regions that were not examined in these studies.

Subsequent to epitope mapping, the antibodies were tested by FACS analysis on a cell line that stably expressed P503S to confirm that the antibodies bind to  
30 cell surface epitopes. Cells stably transfected with a control plasmid were employed as

a negative control. Cells were stained live with no fixative. 0.5 ug of anti-P503S monoclonal antibody was added and cells were incubated on ice for 30 min before being washed twice and incubated with a FITC-labelled goat anti-rabbit or mouse secondary antibody for 20 min. After being washed twice, cells were analyzed with an Excalibur  
5 fluorescent activated cell sorter. The monoclonal antibodies 1C3, 1D12, 9C12, 20D4 and JA1, but not 8D3, were found to bind to a cell surface epitope of P503S.

In order to determine which tissues express P503S, immunohistochemical analysis was performed, essentially as described above, on a panel of normal tissues (prostate, adrenal, breast, cervix, colon, duodenum, gall bladder,  
10 ileum, kidney, ovary, pancreas, parotid gland, skeletal muscle, spleen and testis). HRP-labeled anti-mouse or anti-rabbit antibody followed by incubation with TMB was used to visualize P503S immunoreactivity. P503S was found to be highly expressed in prostate tissue, with lower levels of expression being observed in cervix, colon, ileum and kidney, and no expression being observed in adrenal, breast, duodenum, gall  
15 bladder, ovary, pancreas, parotid gland, skeletal muscle, spleen and testis.

Western blot analysis was used to characterize anti-P503S monoclonal antibody specificity. SDS-PAGE was performed on recombinant (rec) P503S expressed in and purified from bacteria and on lysates from HEK293 cells transfected with full length P503S. Protein was transferred to nitrocellulose and then Western blotted with  
20 each of the anti-P503S monoclonal antibodies (20D4, JA1, 1D12, 6D12 and 9C12) at an antibody concentration of 1 ug/ml. Protein was detected using horse radish peroxidase (HRP) conjugated to either a goat anti-mouse monoclonal antibody or to protein A-sepharose. The monoclonal antibody 20D4 detected the appropriate molecular weight 14 kDa recombinant P503S (amino acids 113-241) and the 23.5 kDa  
25 species in the HEK293 cell lysates transfected with full length P503S. Other anti-P503S monoclonal antibodies displayed similar specificity by Western blot.

#### d) Preparation and Characterization of Antibodies against P703P

Rabbits were immunized with either a truncated (P703Ptr1; SEQ ID NO: 172) or full-length mature form (P703Pfl; SEQ ID NO: 523) of recombinant P703P

protein was expressed in and purified from bacteria as described above. Affinity purified polyclonal antibody was generated using immunogen P703Pfl or P703Ptrl attached to a solid support. Rabbit monoclonal antibodies were isolated using SLAM technology at Immgenics Pharmaceuticals. Table VII below lists both the polyclonal and monoclonal antibodies that were generated against P703P.

Table VII

Antibody	Immunogen	Species/type
Aff. Purif. P703P (truncated); #2594	P703Ptrl	Rabbit polyclonal
Aff. Purif. P703P (full length); #9245	P703Pfl	Rabbit polyclonal
2D4	P703Ptrl	Rabbit monoclonal
8H2	P703Ptrl	Rabbit monoclonal
7H8	P703Ptrl	Rabbit monoclonal

The DNA sequences encoding the complementarity determining regions (CDRs) for the rabbit monoclonal antibodies 8H2, 7H8 and 2D4 were determined and are provided in SEQ ID NO: 506-508, respectively.

Epitope mapping studies were performed as described above. Monoclonal antibodies 2D4 and 7H8 were found to specifically bind to the peptides of SEQ ID NO: 509 (corresponding to amino acids 145-159 of SEQ ID NO: 172) and SEQ ID NO: 510 (corresponding to amino acids 11-25 of SEQ ID NO: 172), respectively. The polyclonal antibody 2594 was found to bind to the peptides of SEQ ID NO: 511-514, with the polyclonal antibody 9427 binding to the peptides of SEQ ID NO: 515-517.

The specificity of the anti-P703P antibodies was determined by Western blot analysis as follows. SDS-PAGE was performed on (1) bacterially expressed recombinant antigen; (2) lysates of HEK293 cells and Ltk<sup>-/-</sup> cells either untransfected or transfected with a plasmid expressing full length P703P; and (3) supernatant isolated from these cell cultures. Protein was transferred to nitrocellulose and then Western blotted using the anti-P703P polyclonal antibody #2594 at an antibody concentration of 1 ug/ml. Protein was detected using horse radish peroxidase (HRP) conjugated to an anti-rabbit antibody. A 35 kDa immunoreactive band could be observed with

recombinant P703P. Recombinant P703P runs at a slightly higher molecular weight since it is epitope tagged. In lysates and supernatants from cells transfected with full length P703P, a 30 kDa band corresponding to P703P was observed. To assure specificity, lysates from HEK293 cells stably transfected with a control plasmid were  
5 also tested and were negative for P703P expression. Other anti-P703P antibodies showed similar results.

Immunohistochemical studies were performed as described above, using anti-P703P monoclonal antibody. P703P was found to be expressed at high levels in normal prostate and prostate tumor tissue but was not detectable in all other tissues  
10 tested (breast tumor, lung tumor and normal kidney).

e) Preparation and Characterization of Antibodies against P504S

Full-length P504S (SEQ ID NO: 108) was expressed and purified from bacteria essentially as described above for P501S and employed to raise rabbit monoclonal antibodies using Selected Lymphocyte Antibody Method (SLAM)  
15 technology at Immgenics Pharmaceuticals (Vancouver, BC, Canada). The anti-P504S monoclonal antibody 13H4 was shown by Western blot to bind to both expressed recombinant P504S and to native P504S in tumor cells.

Immunohistochemical studies using 13H4 to assess P504S expression in various prostate tissues were performed as described above. A total of 104 cases,  
20 including 65 cases of radical prostatectomies with prostate cancer (PC), 26 cases of prostate biopsies and 13 cases of benign prostate hyperplasia (BPH), were stained with the anti-P504S monoclonal antibody 13H4. P504S showed strongly cytoplasmic granular staining in 64/65 (98.5%) of PCs in prostatectomies and 26/26 (100%) of PCs in prostatic biopsies. P504S was stained strongly and diffusely in carcinomas (4+ in  
25 91.2% of cases of PC; 3+ in 5.5%; 2+ in 2.2% and 1+ in 1.1%) and high grade prostatic intraepithelial neoplasia (4+ in all cases). The expression of P504S did not vary with Gleason score. Only 17/91 (18.7%) of cases of NP/BPH around PC and 2/13 (15.4%) of BPH cases were focally (1+, no 2+ to 4+ in all cases) and weakly positive for P504S in large glands. Expression of P504S was not found in small atrophic glands, postatrophic  
30 hyperplasia, basal cell hyperplasia and transitional cell metaplasia in either biopsies or

prostatectomies. P504S was thus found to be over-expressed in all Gleason scores of prostate cancer (98.5 to 100% of sensitivity) and exhibited only focal positivities in large normal glands in 19/104 of cases (82.3% of specificity). These findings indicate that P504S may be usefully employed for the diagnosis of prostate cancer.

5

## EXAMPLE 19

CHARACTERIZATION OF CELL SURFACE EXPRESSION AND  
CHROMOSOME LOCALIZATION OF THE PROSTATE-SPECIFIC ANTIGEN P501S

10 This example describes studies demonstrating that the prostate-specific antigen P501S is expressed on the surface of cells, together with studies to determine the probable chromosomal location of P501S.

The protein P501S (SEQ ID NO: 113) is predicted to have 11 transmembrane domains. Based on the discovery that the epitope recognized by the anti-  
15 P501S monoclonal antibody 10E3-G4-D3 (described above in Example 17) is intracellular, it was predicted that following transmembrane determinants would allow the prediction of extracellular domains of P501S. Fig. 9 is a schematic representation of the P501S protein showing the predicted location of the transmembrane domains and the intracellular epitope described in Example 17. Underlined sequence represents the  
20 predicted transmembrane domains, bold sequence represents the predicted extracellular domains, and italicized sequence represents the predicted intracellular domains. Sequence that is both bold and underlined represents sequence employed to generate polyclonal rabbit serum. The location of the transmembrane domains was predicted using HHMTOP as described by Tusnady and Simon (Principles Governing Amino  
25 Acid Composition of Integral Membrane Proteins: Applications to Topology Prediction, *J. Mol. Biol.* 283:489-506, 1998).

Based on Fig. 9, the P501S domain flanked by the transmembrane domains corresponding to amino acids 274-295 and 323-342 is predicted to be extracellular. The peptide of SEQ ID NO: 518 corresponds to amino acids 306-320 of  
30 P501S and lies in the predicted extracellular domain. The peptide of SEQ ID NO: 519,



which is identical to the peptide of SEQ ID NO: 518 with the exception of the substitution of the histidine with an asparagine, was synthesized as described above. A Cys-Gly was added to the C-terminus of the peptide to facilitate conjugation to the carrier protein. Cleavage of the peptide from the solid support was carried out using the  
5 following cleavage mixture: trifluoroacetic acid:ethanediol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for two hours, the peptide was precipitated in cold ether. The peptide pellet was then dissolved in 10% v/v acetic acid and lyophilized prior to purification by C18 reverse phase hplc. A gradient of 5-60% acetonitrile (containing 0.05% TFA) in water (containing 0.05% TFA) was used to elute the peptide. The purity  
10 of the peptide was verified by hplc and mass spectrometry, and was determined to be >95%. The purified peptide was used to generate rabbit polyclonal antisera as described above.

Surface expression of P501S was examined by FACS analysis. Cells were stained with the polyclonal anti-P501S peptide serum at 10 µg/ml, washed,  
15 incubated with a secondary FITC-conjugated goat anti-rabbit Ig antibody (ICN), washed and analyzed for FITC fluorescence using an Excalibur fluorescence activated cell sorter. For FACS analysis of transduced cells, B-LCL were retrovirally transduced with P501S. To demonstrate specificity in these assays, B-LCL transduced with an irrelevant antigen (P703P) or nontransduced were stained in parallel. For FACS analysis of  
20 prostate tumor cell lines, Lncap, PC-3 and DU-145 were utilized. Prostate tumor cell lines were dissociated from tissue culture plates using cell dissociation medium and stained as above. All samples were treated with propidium iodide (PI) prior to FACS analysis, and data was obtained from PI-excluding (*i.e.*, intact and non-permeabilized) cells. The rabbit polyclonal serum generated against the peptide of SEQ ID NO: 519  
25 was shown to specifically recognize the surface of cells transduced to express P501S, demonstrating that the epitope recognized by the polyclonal serum is extracellular.

To determine biochemically if P501S is expressed on the cell surface, peripheral membranes from Lncap cells were isolated and subjected to Western blot analysis. Specifically, Lncap cells were lysed using a dounce homogenizer in 5 ml of  
30 homogenization buffer (250 mM sucrose, 10 mM HEPES, 1mM EDTA, pH 8.0, 1

complete protease inhibitor tablet (Boehringer Mannheim)). Lysate samples were spun at 1000 g for 5 min at 4 °C. The supernatant was then spun at 8000g for 10 min at 4 °C. Supernatant from the 8000g spin was recovered and subjected to a 100,000g spin for 30 min at 4 °C to recover peripheral membrane. Samples were then separated by SDS-PAGE and Western blotted with the mouse monoclonal antibody 10E3-G4-D3 (described above in Example 17) using conditions described above. Recombinant purified P501S, as well as HEK293 cells transfected with and over-expressing P501S were included as positive controls for P501S detection. LCL cell lysate was included as a negative control. P501S could be detected in Lncap total cell lysate, the 8000g (internal membrane) fraction and also in the 100,000g (plasma membrane) fraction. These results indicate that P501S is expressed at, and localizes to, the peripheral membrane.

To demonstrate that the rabbit polyclonal antiserum generated to the peptide of SEQ ID NO: 519 specifically recognizes this peptide as well as the corresponding native peptide of SEQ ID NO: 518, ELISA analyses were performed. For these analyses, flat-bottomed 96 well microtiter plates were coated with either the peptide of SEQ ID NO: 519, the longer peptide of SEQ ID NO: 520 that spans the entire predicted extracellular domain, the peptide of SEQ ID NO: 521 which represents the epitope recognized by the P501S-specific antibody 10E3-G4-D3, or a P501S fragment (corresponding to amino acids 355-526 of SEQ ID NO: 113) that does not include the immunizing peptide sequence, at 1 µg/ml for 2 hours at 37 °C. Wells were aspirated, blocked with phosphate buffered saline containing 1% (w/v) BSA for 2 hours at room temperature and subsequently washed in PBS containing 0.1% Tween 20 (PBST). Purified anti-P501S polyclonal rabbit serum was added at 2 fold dilutions (1000 ng - 125 ng) in PBST and incubated for 30 min at room temperature. This was followed by washing 6 times with PBST and incubating with HRP-conjugated goat anti-rabbit IgG (H+L) Affinipure F(ab') fragment at 1:20000 for 30 min. Plates were then washed and incubated for 15 min in tetramethyl benzidine. Reactions were stopped by the addition of 1N sulfuric acid and plates were read at 450 nm using an ELISA plate reader. As shown in Fig. 11, the anti-P501S polyclonal rabbit serum specifically recognized the

peptide of SEQ ID NO: 519 used in the immunization as well as the longer peptide of SEQ ID NO: 520, but did not recognize the irrelevant P501S-derived peptides and fragments.

In further studies, rabbits were immunized with peptides derived from the P501S sequence and predicted to be either extracellular or intracellular, as shown in Fig. 9. Polyclonal rabbit sera were isolated and polyclonal antibodies in the serum were purified, as described above. To determine specific reactivity with P501S, FACS analysis was employed, utilizing either B-LCL transduced with P501S or the irrelevant antigen P703P, of B-LCL infected with vaccinia virus-expressing P501S. For surface expression, dead and non-intact cells were excluded from the analysis as described above. For intracellular staining, cells were fixed and permeabilized as described above. Rabbit polyclonal serum generated against the peptide of SEQ ID NO: 548, which corresponds to amino acids 181-198 of P501S, was found to recognize a surface epitope of P501S. Rabbit polyclonal serum generated against the peptide SEQ ID NO: 551, which corresponds to amino acids 543-553 of P501S, was found to recognize an epitope that was either potentially extracellular or intracellular since in different experiments intact or permeabilized cells were recognized by the polyclonal sera. Based on similar deductive reasoning, the sequences of SEQ ID NO: 541-547, 549 and 550, which correspond to amino acids 109-122, 539-553, 509-520, 37-54, 342-359, 295-323, 217-274, 143-160 and 75-88, respectively, of P501S, can be considered to be potential surface epitopes of P501S recognized by antibodies.

In further studies, mouse monoclonal antibodies were raised against amino acids 296 to 322 to P501S, which are predicted to be in an extracellular domain. A/J mice were immunized with P501S/adenovirus, followed by subsequent boosts with an *E. coli* recombinant protein, referred to as P501N, that contains amino acids 296 to 322 of P501S, and with peptide 296-322 (SEQ ID NO: 755) coupled with KLH. The mice were subsequently used for splenic B cell fusions to generate anti-peptide hybridomas. The resulting 3 clones, referred to as 4F4 (IgG1,kappa), 4G5 (IgG2a,kappa) and 9B9 (IgG1,kappa), were grown for antibody production. The 4G5 mAb was purified by passing the supernatant over a Protein A-sepharose column,

followed by antibody elution using 0.2M glycine, pH 2.3. Purified antibody was neutralized by the addition of 1M Tris, pH 8, and buffer exchanged into PBS.

For ELISA analysis, 96 well plates were coated with P501S peptide 296-322 (referred to as P501-long), an irrelevant P775 peptide, P501S-N, P501TR2, P501S-long-KLH, P501S peptide 306-319 (referred to as P501-short)-KLH, or the irrelevant peptide 2073-KLH, all at a concentration of 2 ug/ml and allowed to incubate for 60 minutes at 37 °C. After coating, plates were washed 5X with PBS + 0.1% Tween and then blocked with PBS, 0.5% BSA, 0.4% Tween20 for 2 hours at room temperature. Following the addition of supernatants or purified mAb, the plates were incubated for 60 minutes at room temperature. Plates were washed as above and donkey anti-mouse IgHRP-linked secondary antibody was added and incubated for 30 minutes at room temperature, followed by a final washing as above. TMB peroxidase substrate was added and incubated 15 minutes at room temperature in the dark. The reaction was stopped by the addition of 1N H<sub>2</sub>SO<sub>4</sub> and the OD was read at 450 nM. All three hybrid clones secreted mAb that recognized peptide 296-322 and the recombinant protein P501N.

For FACS analysis, HEK293 cells were transiently transfected with a P501S/VR1012 expression constructs using Fugene 6 reagent. After 2 days of culture, cells were harvested and washed, then incubated with purified 4G5 mAb for 30 minutes on ice. After several washes in PBS, 0.5% BSA, 0.01% azide, goat anti-mouse Ig-FITC was added to the cells and incubated for 30 minutes on ice. Cells were washed and resuspended in wash buffer including 1% propidium iodide and subjected to FACS analysis. The FACS analysis confirmed that amino acids 296-322 of P501S are in an extracellular domain and are cell surface expressed.

The chromosomal location of P501S was determined using the GeneBridge 4 Radiation Hybrid panel (Research Genetics). The PCR primers of SEQ ID NO: 528 and 529 were employed in PCR with DNA pools from the hybrid panel according to the manufacturer's directions. After 38 cycles of amplification, the reaction products were separated on a 1.2% agarose gel, and the results were analyzed through the Whitehead Institute/MIT Center for Genome Research web server

(<http://www-genome.wi.mit.edu/cgi-bin/contig/rhmapper.pl>) to determine the probable chromosomal location. Using this approach, P501S was mapped to the long arm of chromosome 1 at WI-9641 between q32 and q42. This region of chromosome 1 has been linked to prostate cancer susceptibility in hereditary prostate cancer (Smith *et al.* *Science* 274:1371-1374, 1996 and Berthon *et al.* *Am. J. Hum. Genet.* 62:1416-1424, 1998). These results suggest that P501S may play a role in prostate cancer malignancy.

#### EXAMPLE 20

##### REGULATION OF EXPRESSION OF THE PROSTATE-SPECIFIC ANTIGEN P501S

10

Steroid (androgen) hormone modulation is a common treatment modality in prostate cancer. The expression of a number of prostate tissue-specific antigens have previously been demonstrated to respond to androgen. The responsiveness of the prostate-specific antigen P501S to androgen treatment was examined in a tissue culture system as follows.

15

Cells from the prostate tumor cell line LNCaP were plated at  $1.5 \times 10^6$  cells/T75 flask (for RNA isolation) or  $3 \times 10^5$  cells/well of a 6-well plate (for FACS analysis) and grown overnight in RPMI 1640 media containing 10% charcoal-stripped fetal calf serum (BRL Life Technologies, Gaithersburg, MD). Cell culture was continued for an additional 72 hours in RPMI 1640 media containing 10% charcoal-stripped fetal calf serum, with 1 nM of the synthetic androgen Methyltrienolone (R1881; New England Nuclear) added at various time points. Cells were then harvested for RNA isolation and FACS analysis at 0, 1, 2, 4, 8, 16, 24, 28 and 72-hours post androgen addition. FACS analysis was performed using the anti-P501S antibody 10E3-G4-D3 and permeabilized cells.

20

For Northern analysis, 5-10 micrograms of total RNA was run on a formaldehyde denaturing gel, transferred to Hybond-N nylon membrane (Amersham Pharmacia Biotech, Piscataway, NJ), cross-linked and stained with methylene blue. The filter was then prehybridized with Church's Buffer (250 mM  $\text{Na}_2\text{HPO}_4$ , 70 mM  $\text{H}_3\text{PO}_4$ , 1 mM EDTA, 1% SDS, 1% BSA in pH 7.2) at 65 °C for 1 hour. P501S DNA was

25

30

labeled with  $^{32}\text{P}$  using High Prime random-primed DNA labeling kit (Boehringer Mannheim). Unincorporated label was removed using MicroSpin S300-HR columns (Amersham Pharmacia Biotech). The RNA filter was then hybridized with fresh Church's Buffer containing labeled cDNA overnight, washed with 1X SCP (0.1 M NaCl, 0.03 M  $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$ , 0.001 M  $\text{Na}_2\text{EDTA}$ ), 1% sarkosyl (n-lauroylsarcosine) and exposed to X-ray film.

Using both FACS and Northern analysis, P501S message and protein levels were found to increase in response to androgen treatment.

10

## EXAMPLE 20

## PREPARATION OF FUSION PROTEINS OF PROSTATE-SPECIFIC ANTIGENS

The example describes the preparation of a fusion protein of the prostate-specific antigen P703P and a truncated form of the known prostate antigen PSA. The truncated form of PSA has a 21 amino acid deletion around the active serine site. The expression construct for the fusion protein also has a restriction site at 3' end, immediately prior to the termination codon, to aid in adding cDNA for additional antigens.

The full-length cDNA for PSA was obtained by RT-PCR from a pool of RNA from human prostate tumor tissues using the primers of SEQ ID NO: 607 and 608, and cloned in the vector pCR-Blunt II-TOPO. The resulting cDNA was employed as a template to make two different fragments of PSA by PCR with two sets of primers (SEQ ID NO: 609 and 610; and SEQ ID NO: 611 and 612). The PCR products having the expected size were used as templates to make truncated forms of PSA by PCR with the primers of SEQ ID NO: 611 and 613, which generated PSA (delta 208-218 in amino acids). The cDNA for the mature form of P703P with a 6X histidine tag at the 5' end, was prepared by PCR with P703P and the primers of SEQ ID NO: 614 and 615. The cDNA for the fusion of P703P with the truncated form of PSA (referred to as FOPP) was then obtained by PCR using the modified P703P cDNA and the truncated form of PSA cDNA as templates and the primers of SEQ ID NO: 614 and 615. The FOPP

cDNA was cloned into the NdeI site and XhoI site of the expression vector pCRX1, and confirmed by DNA sequencing. The determined cDNA sequence for the fusion construct FOPP is provided in SEQ ID NO: 616, with the amino acid sequence being provided in SEQ ID NO: 617.

5                   The fusion FOPP was expressed as a single recombinant protein in *E. coli* as follows. The expression plasmid pCRX1FOPP was transformed into the *E. coli* strain BL21-CodonPlus RIL. The transformant was shown to express FOPP protein upon induction with 1 mM IPTG. The culture of the corresponding expression clone was inoculated into 25 ml LB broth containing 50 ug/ml kanamycin and 34 ug/ml  
10 chloramphenicol, grown at 37 °C to OD600 of about 1, and stored at 4 °C overnight. The culture was diluted into 1 liter of TB LB containing 50 ug/ml kanamycin and 34 ug/ml chloramphenicol, and grown at 37 °C to OD600 of 0.4. IPTG was added to a final concentration of 1 mM, and the culture was incubated at 30 °C for 3 hours. The cells were pelleted by centrifugation at 5,000 RPM for 8 min. To purify the protein, the  
15 cell pellet was suspended in 25 ml of 10 mM Tris-Cl pH 8.0, 2mM PMSF, complete protease inhibitor and 15 ug lysozyme. The cells were lysed at 4 °C for 30 minutes, sonicated several times and the lysate centrifuged for 30 minutes at 10,000 x g. The precipitate, which contained the inclusion body, was washed twice with 10 mM Tris-Cl pH 8.0 and 1% CHAPS. The inclusion body was dissolved in 40 ml of 10 mM Tris-Cl  
20 pH 8.0, 100 mM sodium phosphate and 8 M urea. The solution was bound to 8 ml Ni-NTA (Qiagen) for one hour at room temperature. The mixture was poured into a 25 ml column and washed with 50 ml of 10 mM Tris-Cl pH 6.3, 100 mM sodium phosphate, 0.5% DOC and 8M urea. The bound protein was eluted with 350 mM imidazole, 10 mM Tris-Cl pH 8.0, 100 mM sodium phosphate and 8 M urea. The fractions containing  
25 FOPP proteins were combined and dialyzed extensively against 10 mM Tris-Cl pH 4.6, aliquoted and stored at - 70 °C.

## EXAMPLE 21

REAL-TIME PCR CHARACTERIZATION OF THE PROSTATE-SPECIFIC ANTIGEN P501S IN  
PERIPHERAL BLOOD OF PROSTATE CANCER PATIENTS

5           Circulating epithelial cells were isolated from fresh blood of normal individuals and metastatic prostate cancer patients, mRNA isolated and cDNA prepared using real-time PCR procedures. Real-time PCR was performed with the Taqman™ procedure using both gene specific primers and probes to determine the levels of gene expression.

10           Epithelial cells were enriched from blood samples using an immunomagnetic bead separation method (Dynal A.S., Oslo, Norway). Isolated cells were lysed and the magnetic beads removed. The lysate was then processed for poly A+ mRNA isolation using magnetic beads coated with Oligo(dT)25. After washing the beads in buffer, bead/poly A+ RNA samples were suspended in 10 mM Tris HCl pH 8.0  
15 and subjected to reversed transcription. The resulting cDNA was subjected to real-time PCR using gene specific primers. Beta-actin content was also determined and used for normalization. Samples with P501S copies greater than the mean of the normal samples + 3 standard deviations were considered positive. Real time PCR on blood samples was performed using the Taqman™ procedure but extending to 50 cycles using  
20 forward and reverse primers and probes specific for P501S. Of the eight samples tested, 6 were positive for P501S and  $\beta$ -actin signal. The remaining 2 samples had no detectable  $\beta$ -actin or P501S. No P501S signal was observed in the four normal blood samples tested.

25

## EXAMPLE 22

EXPRESSION OF THE PROSTATE-SPECIFIC ANTIGENS P703P AND P501S IN  
SCID MOUSE-PASSAGED PROSTATE TUMORS

When considering the effectiveness of antigens in the treatment of  
30 prostate cancer, the continued presence of the antigens in tumors during androgen



ablation therapy is important. The presence of the prostate-specific antigens P703P and P501S in prostate tumor samples grown in SCID mice in the presence of testosterone was evaluated as follows.

Two prostate tumors that had metastasized to the bone were removed from patients, implanted into SCID mice and grown in the presence of testosterone. Tumors were evaluated for mRNA expression of P703P, P501S and PSA using quantitative real time PCR with the SYBR green assay method. Expression of P703P and P501S in a prostate tumor was used as a positive control and the absence in normal intestine and normal heart as negative controls. In both cases, the specific mRNA was present in late passage tumors. Since the bone metastases were grown in the presence of testosterone, this implies that the presence of these genes would not be lost during androgen ablation therapy.

#### EXAMPLE 23

##### ANTI-P503S MONOCLONAL ANTIBODY INHIBITS TUMOR GROWTH *IN VIVO*

The ability of the anti-P503S monoclonal antibody 20D4 to suppress tumor formation in mice was examined as follows.

Ten SCID mice were injected subcutaneously with HEK293 cells that expressed P503S. Five mice received 150 micrograms of 20D4 intravenously at day 0 (time of tumor cell injection), day 5 and day 9. Tumor size was measured for 50 days. Of the five animals that received no 20D4, three formed detectable tumors after about 2 weeks which continued to enlarge throughout the study. In contrast, none of the five mice that received 20D4 formed tumors. These results demonstrate that the anti-P503S Mab 20D4 displays potent anti-tumor activity *in vivo*.

#### EXAMPLE 24

##### CHARACTERIZATION OF A T CELL RECEPTOR CLONE FROM A P501S-SPECIFIC T CELL CLONE

T cells have a limited lifespan. However, cloning of T cell receptor (TCR) chains and subsequent transfer essentially enables infinite propagation of the T

cell specificity. Cloning of tumor-antigen TCR chains allows the transfer of the specificity into T cells isolated from patients that share the TCR MHC-restricting allele. Such T cells could then be expanded and used in adoptive transfer settings to introduce the tumor antigen specificity into patients carrying tumors that express the antigen. T cell receptor alpha and beta chains from a CD8 T cell clone specific for the prostate-specific antigen P501S were isolated and sequenced as follows.

Total mRNA from  $2 \times 10^6$  cells from CTL clone 4E5 (described above in Example 12) was isolated using Trizol reagent and cDNA was synthesized. To determine Va and Vb sequences in this clone, a panel of Va and Vb subtype-specific primers was synthesized and used in RT-PCR reactions with cDNA generated from each of the clones. The RT-PCR reactions demonstrated that each of the clones expressed a common Vb sequence that corresponded to the Vb7 subfamily. Furthermore, using cDNA generated from the clone, the Va sequence expressed was determined to be Va6. To clone the full TCR alpha and beta chains from clone 4E5, primers were designed that spanned the initiator and terminator-coding TCR nucleotides. The primers were as follows: TCR Valpha-6 5'(sense): GGATCC---GCCGCCACC---ATGTCACCTTTCTAGCCTGCT (SEQ ID NO: 756) BamHI site Kozak TCR alpha sequence TCR alpha 3' (antisense): GTCGAC---TCAGCTGGACCACAGCCGCAG (SEQ ID NO: 757) SalI site TCR alpha constant sequence TCR Vbeta-7. 5'(sense): GGATCC---GCCGCCACC---ATGGGCTGCAGGCTGCTCT (SEQ ID NO: 758) BamHI site Kozak TCR alpha sequence TCR beta 3' (antisense): GTCGAC---TCAGAAATCCTTTCTCTTGAC (SEQ ID NO: 759) SalI site TCR beta constant sequence. Standard 35 cycle RT-PCR reactions were established using cDNA synthesized from the CTL clone and the above primers, employing the proofreading thermostable polymerase PWO (Roche, Nutley, NJ).

The resultant specific bands (approx. 850 bp for alpha and approx. 950 for beta) were ligated into the PCR blunt vector (Invitrogen) and transformed into *E. coli*. *E. coli* transformed with plasmids containing full-length alpha and beta chains were identified, and large scale preparations of the corresponding plasmids were generated. Plasmids containing full-length TCR alpha and beta chains were submitted

for sequencing. The sequencing reactions demonstrated the cloning of full-length TCR alpha and beta chains with the determined cDNA sequences for the Vb and Va chains being shown in SEQ ID NO: 760 and 761, respectively. The corresponding amino acid sequences are shown in SEQ ID NO: 762 and 763, respectively. The Va sequence was  
5 shown by nucleotide sequence alignment to be 99% identical (347/348) to Va6.2, and the Vb to be 99% identical to Vb7 (336/338).

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration,  
10 various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

## CLAIMS

## What is Claimed:

1. An isolated polynucleotide comprising a sequence selected from the group consisting of:

(a) sequences provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(b) complements of the sequences provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(c) sequences consisting of at least 20 contiguous residues of a sequence provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(d) sequences that hybridize to a sequence provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788 under moderately stringent conditions;

(e) sequences having at least 75% identity to a sequence of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-

375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788;

(f) sequences having at least 90% identity to a sequence of SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788; and

(g) degenerate variants of a sequence provided in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 and 786-788.

2. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 and 789-791;

(b) sequences having at least 70% identity to a sequence of SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 and 789-791;

(c) sequences having at least 90% identity to a sequence of SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380, 383, 477-483, 496, 504, 505, 519, 520, 522, 525, 527, 532, 534, 537-551, 553-568, 573-586, 588-590, 592, 627-

629, 632, 633, 635, 637, 638, 656-671, 675, 683, 684, 710, 712, 714, 715, 717-719, 723-734, 736, 740-750, 752, 754, 755, 766-772, 777-785 and 789-791;

- (d) sequences encoded by a polynucleotide of claim 1;
- (e) sequences having at least 70% identity to a sequence encoded by a polynucleotide of claim 1; and
- (f) sequences having at least 90% identity to a sequence encoded by a polynucleotide of claim 1.

3. An expression vector comprising a polynucleotide of claim 1 operably linked to an expression control sequence.

4. A host cell transformed or transfected with an expression vector according to claim 3.

5. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a polypeptide of claim 2.

6. A method for detecting the presence of a cancer in a patient, comprising the steps of:

- (a) obtaining a biological sample from the patient;
- (b) contacting the biological sample with a binding agent that binds to a polypeptide of claim 2;
- (c) detecting in the sample an amount of polypeptide that binds to the binding agent; and
- (d) comparing the amount of polypeptide to a predetermined cut-off value and therefrom determining the presence of a cancer in the patient.

7. A fusion protein comprising at least one polypeptide according to claim 2.

8. The fusion protein of claim 7, wherein the fusion protein comprises a sequence selected from the group consisting of:

(a) sequences provided in SEQ ID NO: 682, 692, 695, 699, 703 and 709; and

(b) sequences encoded by SEQ ID NO: 679, 691, 696, 700, 704 and 708.

9. An oligonucleotide that hybridizes to a sequence recited in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 and 384-476, 524, 526, 530, 531, 533, 535, 536, 552, 569-572, 587, 591, 593-606, 618-626, 630, 631, 634, 636, 639-655, 674, 680, 681, 711, 713, 716, 720-722, 735, 737-739, 751, 753, 764, 765, 773-776 or 786-788 under moderately stringent conditions.

10. A method for stimulating and/or expanding T cells specific for a tumor protein, comprising contacting T cells with at least one component selected from the group consisting of:

(a) polypeptides according to claim 2;  
(b) polynucleotides according to claim 1; and  
(c) antigen-presenting cells that express a polypeptide according to claim 1,

under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

11. An isolated T cell population, comprising T cells prepared according to the method of claim 10.

12. A composition comprising a first component selected from the group consisting of physiologically acceptable carriers and immunostimulants, and a second component selected from the group consisting of:

- (a) polypeptides according to claim 2;
- (b) polynucleotides according to claim 1;
- (c) antibodies according to claim 5;
- (d) fusion proteins according to claim 7;
- (e) T cell populations according to claim 11; and
- (f) antigen presenting cells that express a polypeptide according to claim 2.

13. A method for stimulating an immune response in a patient, comprising administering to the patient a composition of claim 12.

14. A method for the treatment of a cancer in a patient, comprising administering to the patient a composition of claim 12.

15. A method for determining the presence of a cancer in a patient, comprising the steps of:

- (a) obtaining a biological sample from the patient;
- (b) contacting the biological sample with an oligonucleotide according to claim 9;
- (c) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; and
- (d) compare the amount of polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence of the cancer in the patient.

16. A diagnostic kit comprising at least one oligonucleotide according to claim 9.



17. A diagnostic kit comprising at least one antibody according to claim 5 and a detection reagent, wherein the detection reagent comprises a reporter group.

18. A method for inhibiting the development of a cancer in a patient, comprising the steps of:

(a) incubating CD4+ and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of: (i) polypeptides according to claim 2; (ii) polynucleotides according to claim 1; and (iii) antigen presenting cells that express a polypeptide of claim 2, such that T cell proliferate; and

(b) administering to the patient an effective amount of the proliferated T cells,

thereby inhibiting the development of a cancer in the patient.

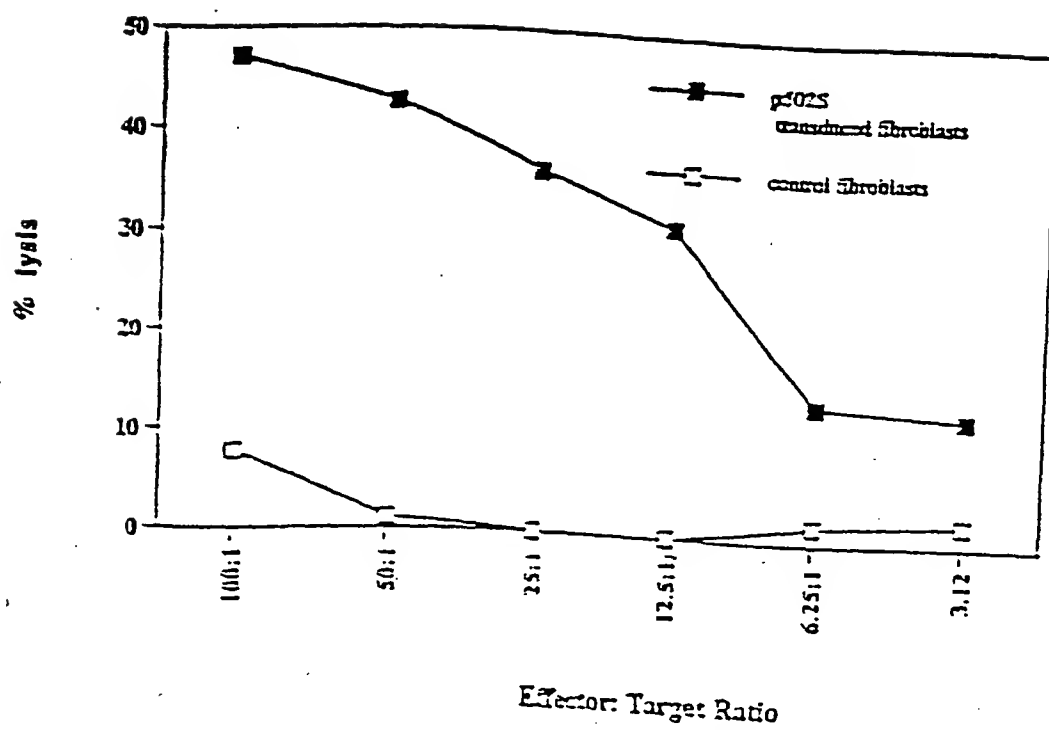


Fig. 1

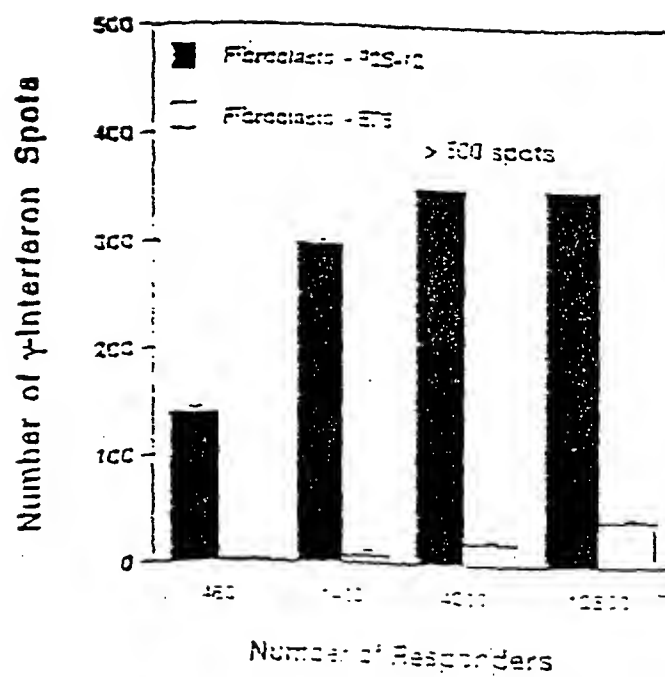


Fig. 2A

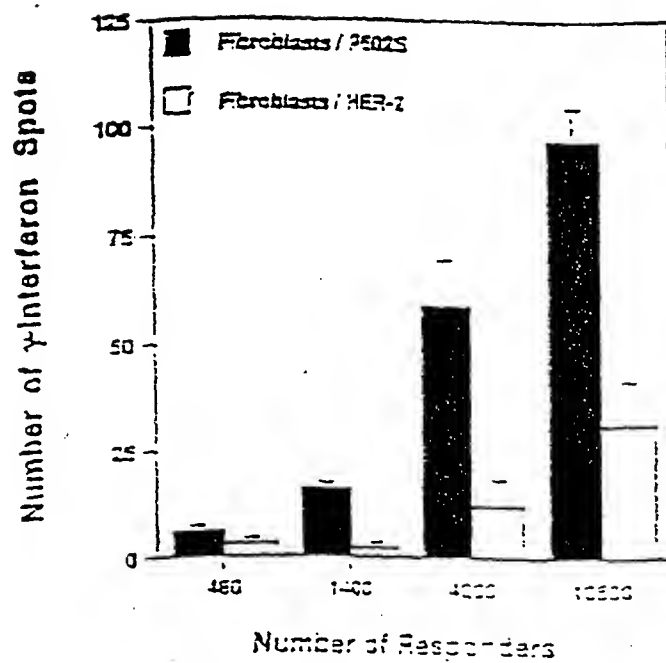


Fig. 25

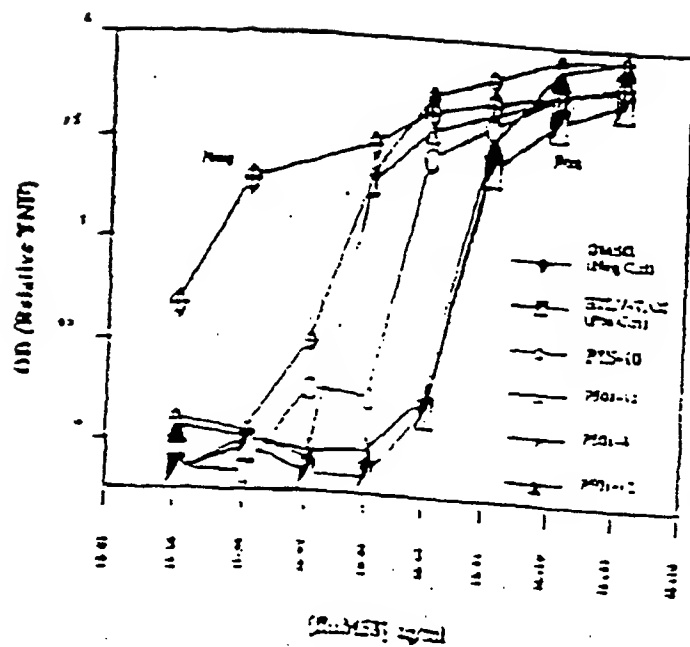


Fig. 3

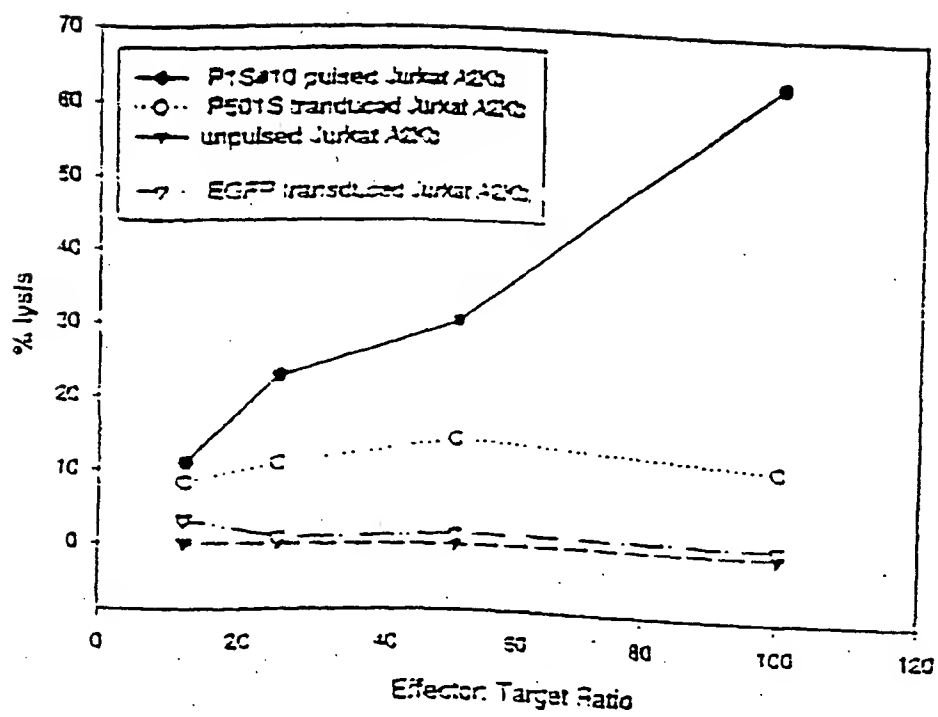


Fig. 4

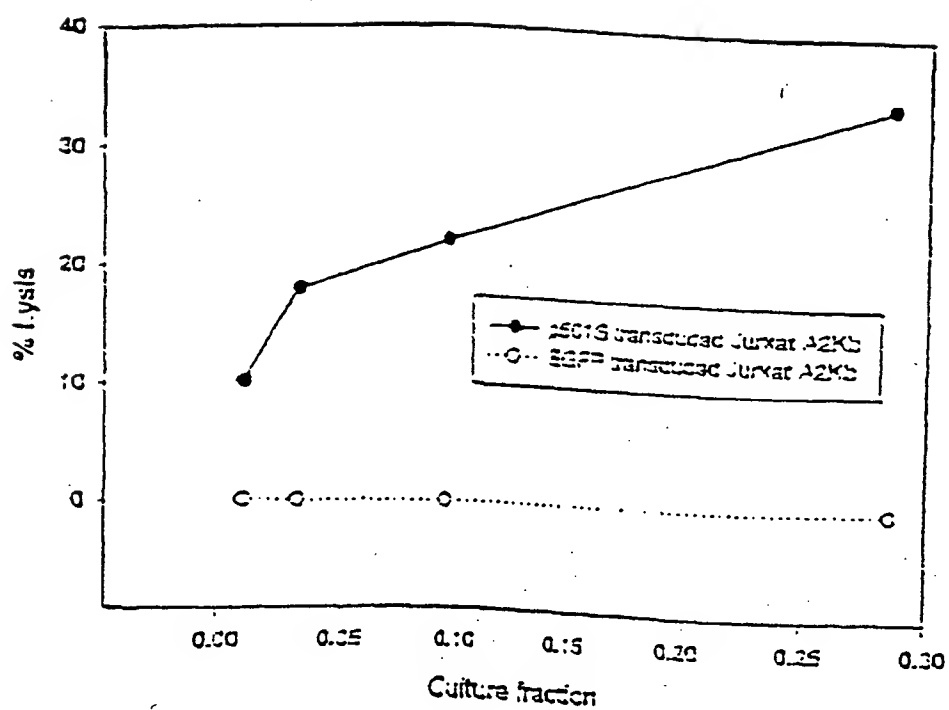


Fig. 5

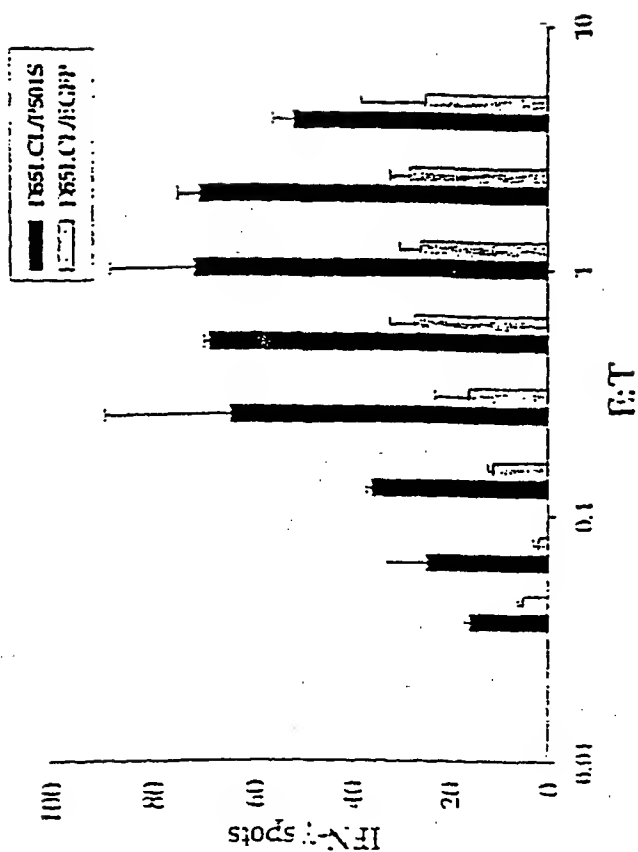


Fig. 6B

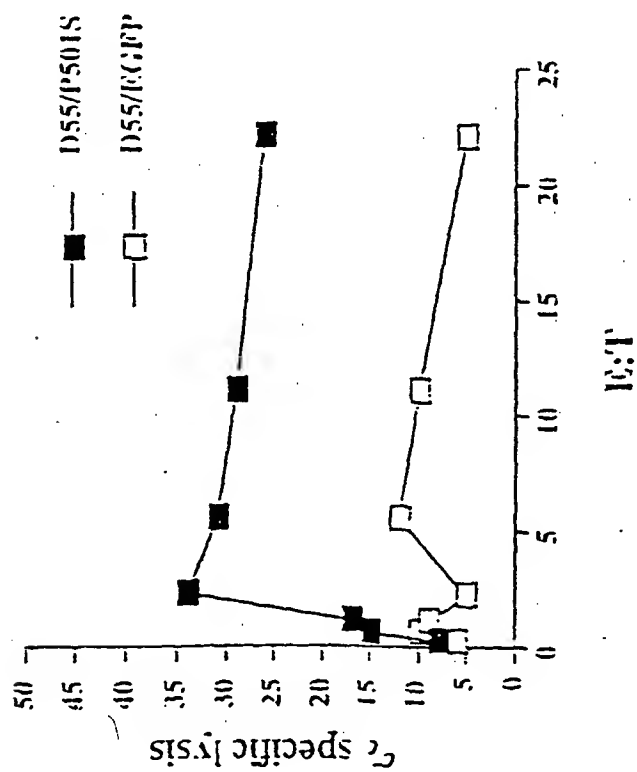
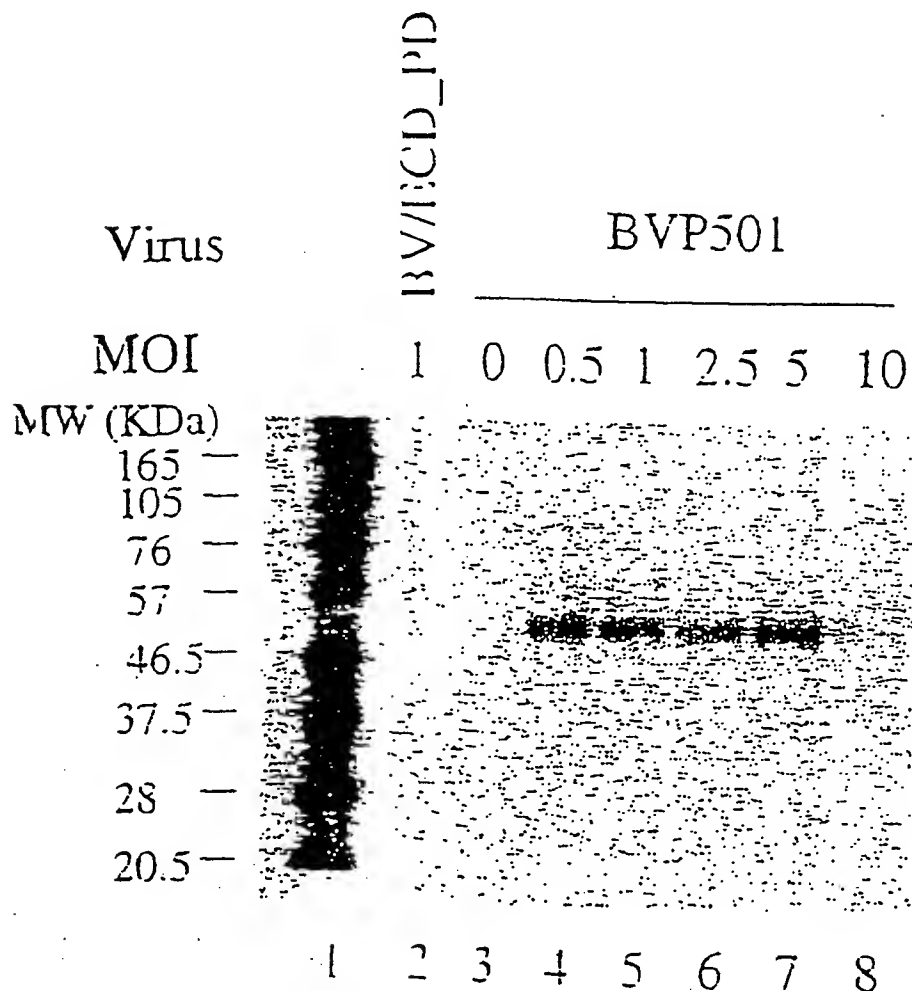


Fig. 6A



# Expression of P501S by the Baculovirus Expression System



0.6 million high 5 cells in 6-well plate were infected with an unrelated control virus BV/ECD\_PD (lane 2), without virus (lane 3), or with recombinant baculovirus for P501 at different MOIs (lane 4-8). Cell lysates were run on SDS-PAGE under the reducing conditions and analyzed by Western blot with a monoclonal antibody against P501S (P501S-10E3-G4D3). Lane 1 is the biotinylated protein molecular weight marker. 5 µg/lane.

Fig. 7

Figure 8. Mapping of the epitope recognized by 10E3-G4-D3

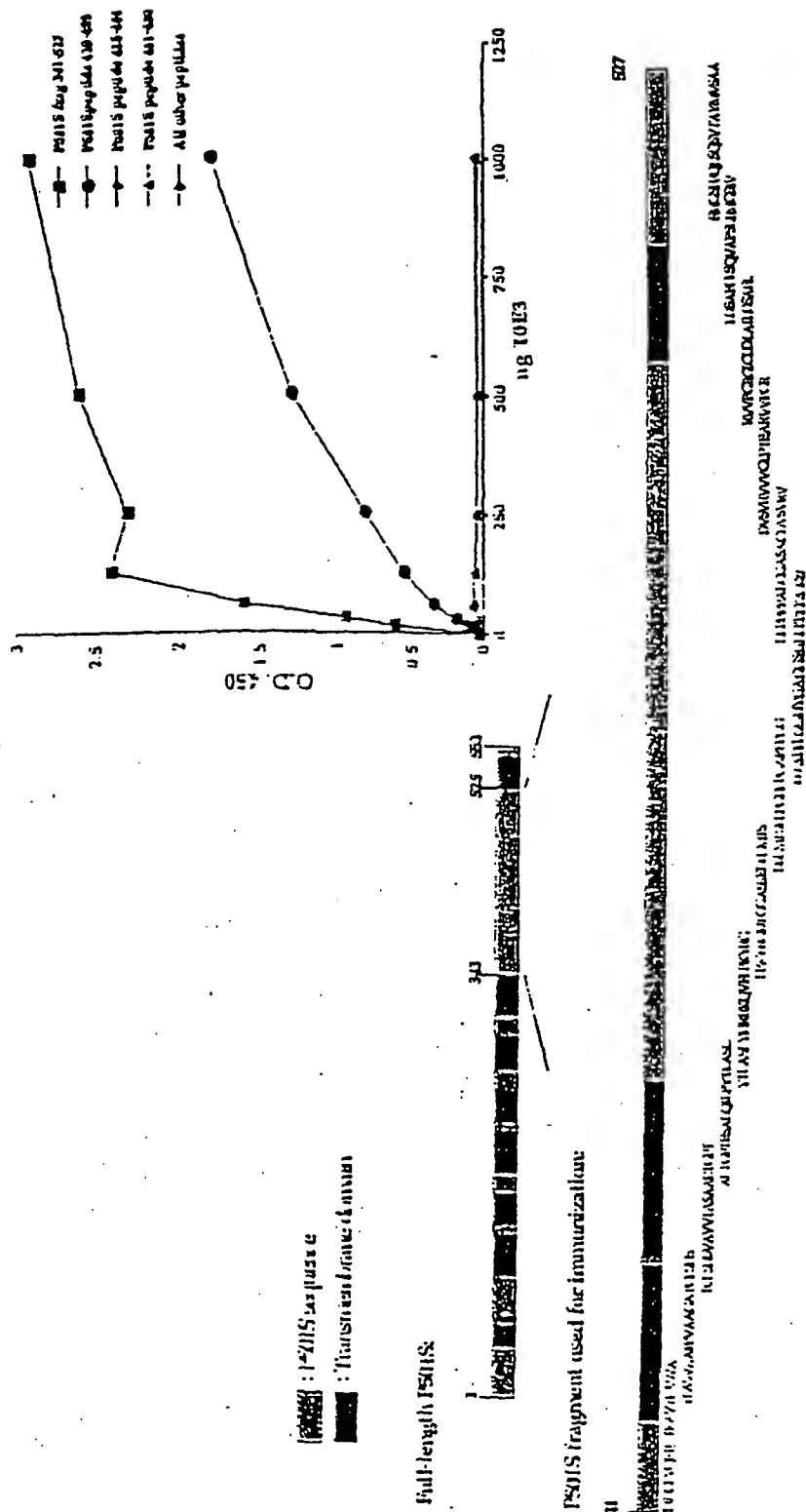


Fig. 8

# Figure 1. Schematic of P501S with predicted transmembrane, cytoplasmic, and extracellular regions

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Underlined sequence: Predicted transmembrane domain; **Bold sequence**: Predicted extracellular domain;  
*Italic sequence*: Predicted intracellular domain. Sequence in bold/underlined: used to generate polyclonal rabbit serum

Localization of domains predicted using IMMTOPI (G.R. Tusnady and I. Simon (1998) Principles  
 Governing Amino Acid Composition of Integral Membrane Proteins: Applications to topology Prediction. J. Mol. Biol. 283,  
 489-506.



**FIGURE 4. Elisa assay of rabbit polyclonal antibody specificity**

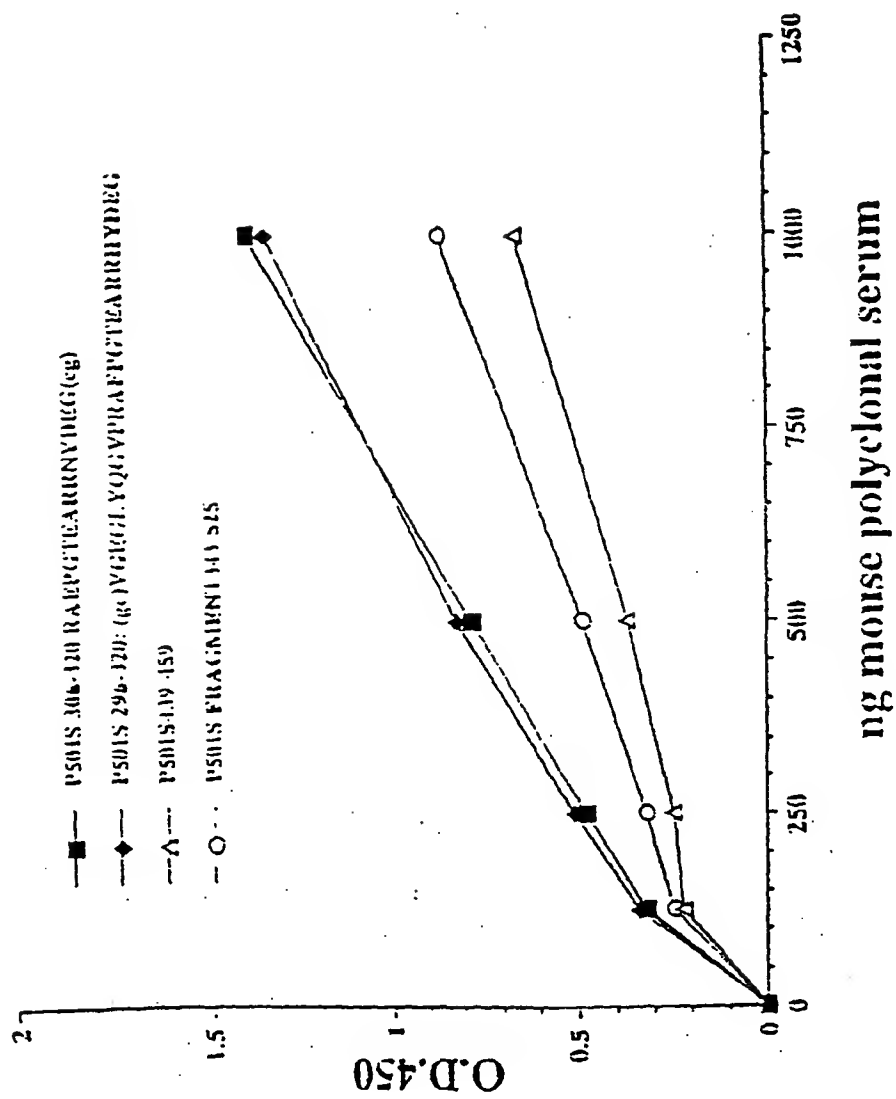


Fig. 11

## SEQUENCE LISTING

<110> Corixa Corporation  
 Smithkline Beechan Biologicals S.A.  
 Xu, Jiangchun  
 Dillon, Davin C.  
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 Harlocker, Susan L.  
 Jiang, Yuqui  
 Reed, Steven G.  
 Kalos, Michael D.  
 Fanger, Gary R.  
 Retter, Marc W.  
 Stolk, John A.  
 Day, Craig H.  
 Skeiky, Yasir A.W.  
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&lt;223&gt; n = A,T,C or G

&lt;400&gt; 8

catttccggg	tttactttct	aaggaaagcc	gagcgggaagc	tgctaacgtg	ggaatcgggtg	60
cataaggaga	actttctgct	ggcacgcgct	agggacaagc	gggagagcga	ctccgagcgt	120
ctgaagcgca	cgtcccagaa	ggtggacttg	gcactgaaac	agctgggaca	catccgcgag	180
tacgaacagc	gcctgaaagt	gctggagcgg	gaggtccagc	agtgtagccg	cgtcctgggg	240

tggttgccg	angcctganc	cgctctgcct	tgttgccccc	angtgggccc	ccacccctg	300
acctgcctg	gtccaaacac	tgagccctgc	tggcggactt	caagganaac	ccccacang	360
ggattttgct	cctanantaa	ggctcatctg	ggcctcggcc	ccccacactg	gttgcccttg	420
tctttgangt	gagcccatg	tccatctggg	ccactgtcng	gaccaccttt	ngggagtgtt	480
ctccttacia	ccacannatg	cccggtcct	cccgaaacc	antccancc	tgngaaggat	540
caagnccctgn	atccactnnt	nctanaaccg	gccnccnccg	cngtggaacc	cnccttntgt	600
tccttttct	tnagggttaa	tnnccgcttg	gccttnccan	ngtcctncnc	ntttccnnt	660
gttnaaattg	ttangcnccc	nccnntcccn	cnnnncnan	cccgaccenn	annttnann	720
ncctgggggt	nccnncngat	tgacccncc	nccctntant	tgcnttnggg	nncnntgccc	780
ctttccctct	nggganncg					799

<210> 9  
 <211> 801  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(801)  
 <223> n = A,T,C or G

<400> 9						
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caaggacaag	gccaccagg	gcgggggccc	aagcccat	gaccttact	ctatgagcaa	180
aatccctgt	gggggcttct	ccttgaagtc	cgccancagg	gctcagtctt	tggacccang	240
caggtcatgg	ggttgtnngc	caactggggg	ccncaacgca	aaanggcnc	gggcctcngn	300
caccatccc	angacgcggc	tacactnctg	gacctccnc	tccaccactt	tcatgcgctg	360
ttcntaccg	cgnatntgtc	ccanctgttt	cngtgccnac	tccancttct	nggacgtggg	420
ctacatacgc	ccggantcnc	nctcccgtt	tgtccctatc	cacgtncan	caacaaattt	480
cncntantg	caccnatcc	cacntttnc	agntttcnc	nncngcttc	cttntaaaag	540
ggttganccc	cggaaaatnc	cccaaagggg	gggggcccng	taccaactn	ccccctnata	600
gctgaantcc	ccatnaccnn	gnctcnatgg	ancntccnt	tttaannacn	ttctnaactt	660
gggaanance	ctcgnccntn	ccccnttaa	tccnccctg	cnangnnct	cccccnctcc	720
nccnntng	gcntntnann	cnaaaaaggc	ccnnnanc	tctcctnncn	cctcanttgc	780
ccanccctgc	aatcggccn	c				801

<210> 10  
 <211> 789  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(789)  
 <223> n = A,T,C or G

<400> 10						
cagtctatnt	ggccagtgtg	gcagctttcc	ctgtggctgc	cggtgccaca	tgctgtccc	60
acagtgtggc	cgtggtgaca	gcttcagccg	ccctcaccgg	gttcaccttc	tcagccctgc	120
agatccctgc	ctacacactg	gcctccctct	accaccggga	gaagcaggtg	ttcctgccca	180
aataccgagg	ggacactgga	ggtgctagca	gtgaggacag	cctgatgacc	agcttccctg	240
caggccctaa	gcctggagct	cccttcccta	atggacacgt	gggtgctgga	ggcagtgccc	300
tgctcccacc	tccaccgcg	ctctgcgggg	cctctgcctg	tgatgtctcc	gtacgtgtgg	360
tggtgggtga	gccaccgan	gccagggtgg	ttccgggccc	gggcatctgc	ctggacctcg	420
ccatccctgga	tagtgcttcc	tgctgtccca	ngtggcccca	tccctgttta	tgggctccat	480
tgccagctc	agccagctctg	tactgccta	tatggtgtct	gccgcaggcc	tgggtctggt	540
ccatttact	ttgctacaca	ggtantattt	gacaagaacg	anttggccaa	atactcagcg	600

ttaaaaaatt	ccagcaacat	tgggggtgga	aggcctgcct	cactgggtcc	aactccccgc	660
tcctgttaac	cccatggggc	tgccggcttg	gccgccatt	tctgttctg	ccaaantnat	720
gtggctctct	gctgccacct	gttgctggct	gaagtgcnta	cngcncanct	nggggggtng	780
gnggttccc						789

<210> 11  
 <211> 772  
 <212> DNA  
 <213> Homo sapien  
  
 <220>  
 <221> misc\_feature  
 <222> (1)...(772)  
 <223> n = A,T,C or G

<400> 11						
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accaacaggc	cacatcctga	taaaaggtaa	gaggggggtg	gatcagcaaa	aagacagtgc	180
tgtgggctga	ggggacctgg	ttcttgtgtg	ttgcccctca	ggactcttcc	cctacaaata	240
actttcatat	gttcaaattcc	catggaggag	tgtttcatcc	tagaaactcc	catgcaagag	300
ctacattaaa	cgaagctgca	ggtaagggg	cttanagatg	ggaaaccagg	tgactgagtt	360
tattcagctc	ccaaaaaccc	ttctctaggt	gtgtctcaac	taggaggcta	gctgttaacc	420
ctgagcctgg	gtaatccacc	tgagagtgcc	ccgcattcca	gtgcatggaa	cccttctggc	480
ctccctgtat	aagtccagac	tgaaaccccc	ttggaaggnc	tccagtcagg	cagccctana	540
aactggggaa	aaaagaaaag	gacgccccan	ccccagctg	tgcanctacg	cacctcaaca	600
gcacaggggtg	gcagcaaaaa	aaccacttta	ctttggcaca	aacaaaaact	ngggggggca	660
accccgccac	cccnangggg	gttaacagga	ancngggnaa	cntggaaccc	aattnaggca	720
ggcccnccac	ccnnaatntt	gctgggaaat	ttttctctcc	ctaaatnttt	tc	772

<210> 12  
 <211> 751  
 <212> DNA  
 <213> Homo sapien  
  
 <220>  
 <221> misc\_feature  
 <222> (1)...(751)  
 <223> n = A,T,C or G

<400> 12						
gccccaatte	cagctgccac	accacccacg	gtgactgcac	tagttcggat	gtcatacaaa	60
agctgattga	agcaaccctc	tacttttttg	togtgagcct	tttgcttggt	gcaggtttca	120
ttggctgtgt	tggtgacgtt	gtcattgcaa	cagaatgggg	gaaaggcact	gttctctttg	180
aagtanggtg	agtcctcaaa	atccgtatag	ttgggtgaagc	cacagcactt	gagcccttcc	240
atggtggtgt	tccacacttg	agtgaagtct	tcctgggaac	cataatcttt	cttgatggca	300
ggcactacca	gcaacgtcag	ggaagtgtc	agccattgtg	gtgtacacca	aggcgaccac	360
agcagctgcn	acctcagcaa	tgaagatgan	gaggangatg	aagaagaacg	tcncgagggc	420
acacttgctc	tcagtcttan	caccatanca	gcccntgaaa	accaananca	aagaccacna	480
cnccggctgc	gatgaagaaa	tnaccccneg	ttgacaaact	tgcatggcac	tggganccac	540
agtggcccna	aaaatcttca	aaaaggatgc	cccatcnatt	gaccccccaa	atgccactcg	600
ccaacagggg	ctgccccacn	cncnnaacga	tgancnatt	gnacaagatc	tncttggtct	660
tnatnaacnt	gaacctgcn	tngtggctcc	tgttcaggnc	cnnggcctga	cttctnaann	720
aangaactcn	gaagncccca	cngganannc	g			751

<210> 13  
 <211> 729  
 <212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(729)

<223> n = A,T,C or G

<400> 13

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tgtggancct	cagcagtncc	ctctttcaga	actcantgcc	aaganccctg	aacaggagcc	120
accatgcagt	gcttcagctt	cattaagacc	atgatgatcc	tottcaattt	gctcatcttt	180
ctgtgtggtg	cagccctgtt	ggcagtgggc	atctgggtgt	caatcgatgg	ggcatccttt	240
ctgaagatct	tcgggccact	gtcgtccagt	gccatgcagt	ttgtcaacgt	gggctacttc	300
ctcatcgag	ccggcggtgt	ggtcttagct	ctaggtttcc	tgggtgcta	tgggtgctaag	360
actgagagca	agtgtgccct	cgtgacgttc	ttcttcaccc	tcctcctcat	cttcattgct	420
gaggttgcaa	tgctgtggtc	gccttggtgt	acaccacaat	ggctgagcac	ttcctgacgt	480
tgctggtaat	gcctgccatc	aanaaaagat	tatgggttcc	caggaaact	tcactcaagt	540
gttggaacac	caccatgaaa	gggtcaagt	gctgtggctt	cnnccaacta	tacggatttt	600
gaagantcac	ctacttcaaa	gaaaanagtg	cctttccccc	atttctgttg	caattgacaa	660
acgtcccaa	cacagccaat	tgaaaacctg	caccaaccc	aaanggtcc	ccaaccanaa	720
attnaaggg						729

<210> 14

<211> 816

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(816)

<223> n = A,T,C or G

<400> 14

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tgctcgctga	aggggttgta	gtaccagcgc	gggatgctct	ccttgagag	tcctgtgtct	120
ggcaggtcca	cgcagtgcc	tttgtcactg	gggaaatgga	tgcgctggag	ctcgtcaaag	180
ccactcgtgt	atttttcaca	ggcagcctcg	tccgacgcgt	cggggcagtt	gggggtgtct	240
tcacactcca	ggaaactgtc	natgcagcag	ccattgctgc	agcggaactg	ggtgggtgta	300
cangtgccag	agcacactgg	atggcgctt	tccatggnan	gggcccctng	ggaaagtccc	360
tganccccc	anctgcctct	caaangcccc	accttgacac	ccccgacagg	ctagaatgga	420
atcttcttcc	cgaaaggtag	ttnttcttgt	tgcccaancc	anccccntaa	acaaactctt	480
gcanatctgc	tccngggggg	tctantacc	ancgtgggaa	agaacccca	ggcngcgaac	540
caancttggt	tgatnccgaa	gcnataatct	nctnttctgc	ttggtggaca	gcaccantna	600
ctgtnnanct	ttagnccntg	gtcctcntgg	gttgnncttg	aacctaatcn	ccntcaact	660
gggacaaggt	aantngccnt	cctttnaatt	cccnancntn	ccccctggtt	tggggttttn	720
cncnctccta	ccccagaaan	nccgtgttcc	cccccaacta	ggggccnaaa	ccnntnttc	780
cacaacctn	ccccacccac	gggttcngnt	ggttng			816

<210> 15

<211> 783

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(783)

<223> n = A,T,C or G

## &lt;400&gt; 15

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atgtggaaaa	cacagattgg	cgctactgc	ggggtgacac	ggatgtcagg	gtagagagga	120
aagacccaaa	ccaggtggaa	ctgtggggac	tcaaggaang	cacctacctg	ttccagctga	180
cagtgactag	ctcagaccac	ccagaggaca	cggccaacgt	cacagtcact	gtgctgtcca	240
ccaagcagac	agaagactac	tgcctcgcat	ccaacaangt	gggtcgctgc	cggggctctt	300
tcccacgctg	gtactatgac	cccacggagc	agatctgcaa	gagtttcgtt	tatggaggct	360
gcttgggcaa	caagaacaac	taccttcggg	aagaagagtg	cattctancc	tgtcnggggtg	420
tgcaagggtg	gcctttgana	ngcanctctg	gggctcangc	gactttcccc	cagggccctt	480
ccatggaaag	gcgccatcca	ntgttctctg	gcacctgtca	gcccaccag	ttccgctgca	540
ncaatggctg	ctgcatcnac	antttcctng	aattgtgaca	acacccccca	ntgcccccaa	600
ccctcccaac	aaagcttccc	tgttnaaaaa	tacnccantt	ggcttttnac	aaacnccggg	660
cncctccttt	ttccccnntn	aacaaagggc	nctngcnttt	gaactgcccn	aaccnnggaa	720
tctnccnngg	aaaaantncc	ccccctggtt	cctnnaancc	cctcncnaa	anctncccc	780
ccc						783

&lt;210&gt; 16

&lt;211&gt; 801

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(801)

&lt;223&gt; n = A,T,C or G

## &lt;400&gt; 16

gccccaatte	cagctgccac	accacccacg	gtgactgcat	tagttcggat	gtcatacaaa	60
agctgattga	agcaaccctc	tacttttttg	tcgtgagcct	tttgcttggg	gcaggtttca	120
ttggctgtgt	tggtgacgtt	gtcattgcaa	cagaatgggg	gaaaggcact	gttctctttg	180
aagtagggtg	agtccctcaa	atccgtatag	ttggtgaagc	cacagcactt	gagcccttc	240
atggtggtgt	tccacacttg	agtgaagtct	tcctgggaac	cataatcttt	cttgatggca	300
ggcactacca	gcaacgtcag	gaagtgtctc	gccattgtgg	tgtacacca	ggcgaccaca	360
gcagctgcaa	cctcagcaat	gaagatgagg	aggaggatga	agaagaacgt	cncgagggca	420
cacttgctct	ccgtcttagc	accatagcag	cccangaaac	caagagcaaa	gaccacaacg	480
cngctgcga	atgaaagaaa	ntaccacacgt	tgacaaaactg	catggccact	ggacgacagt	540
tggcccgaa	atcttcagaa	aagggtatgcc	ccatcgattg	aacacccana	tgcccactgc	600
cnacagggtc	gcncncncn	gaaagaatga	gccattgaag	aaggatcctc	ntggtcttaa	660
tgaactgaaa	ccttgcatgg	tggccctctg	tcagggtctc	tggcagtgaa	ttctganaaa	720
aaggaacngc	ntnagcccc	ccaaangana	aaacaccccc	gggtgttgcc	ctgaattggc	780
ggccaaggan	ccctgccccn	g				801

&lt;210&gt; 17

&lt;211&gt; 740

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(740)

&lt;223&gt; n = A,T,C or G

## &lt;400&gt; 17

gtgagagcca	ggcgtccctc	tgctgcccc	ctcagtggca	acacccggga	gctgttttgt	60
cctttgtgga	gcctcagcag	ttccctcttt	cagaactcac	tgccaagagc	cctgaacagg	120
agccaccatg	cagtgtctca	gcttcattaa	gaccatgatg	atcctcttca	atttgctcat	180
ctttctgtgt	ggtgcagccc	tgttggcagt	gggcatctgg	gtgtcaatcg	atggggcatc	240
ctttctgaag	atcttcgggc	cactgtcgtc	cagtgccatg	cagtttgtca	acgtgggcta	300

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cttcctcatc gcagccggcg ttgtggtctt tgetcttggg ttcctgggct gctatggtgc 360
taagacggag agcaagtgtg ccctcgtgac gttcttcttc atcctcctcc tcatcttcat 420
tgctgaagtt gcagctgctg tggcgcctt ggtgtacacc acaatggctg aaccattcct 480
gacgttgctg gtantgcctg ccatcaanaa agattatggg ttcccaggaa aaattcactc 540
aantntggaa caccnccatg aaaagggctc caatttctgn tggcttcccc aactataccg 600
gaattttgaa agantcnccc tacttccaaa aaaaaanant tgcctttnc cccnttctgt 660
tgcaatgaaa acntcccaan acngccaatn aaaacctgcc cnnncaaaaa ggntcncaaa 720
caaaaaaant nnaagggttn

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<210> 18
<211> 802
<212> DNA
<213> Homo sapien

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<220>
<221> misc_feature
<222> (1)...(802)
<223> n = A,T,C or G

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<400> 18
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caaggtcttc cagctgccgc acattacgca gggcaagagc ctccagcaac actgcatatg 120
ggatacactt tactttagca gccaggggtg caactgagag gtgtcgaagc ttattcttct 180
gagctctctg tagtgagga agattccggg cttagctaa gtatgcagcg tatgtcccat 240
aagcaaacac tgtgagcagc cggaaggtag aggcaaagtc actctcagcc agctctctaa 300
cattgggcat gtccagcagt tctccaaaca cgtagacacc agnggcctcc agcacctgat 360
ggatgagtgt ggccagcgct gccccttgg ccgacttggc taggagcaga aattgctcct 420
ggttctgccc tgtcaccttc acttcgcgac tcatcactgc actgagtgtg ggggacttgg 480
gctcaggatg tccagagacg tggttccgcc cctcnctta atgacaccgn ccanncaacc 540
gtcggctccc gcogantng ttcgtcgtnc ctgggtcagg gtctgctggc cncacttgc 600
aanctctgtc nggcccatgg aattcaccnc accggaactn gtangatcca ctnttctat 660
aaccgngcgc caccgcnntt ggaactccac tcttnttnc tttacttgag ggttaaggtc 720
acccttncg ttaccttggg ccaaaccntn cntgtgtcg anantngtna tcnngnccna 780
tnccanccnc atangaagcc ng
802

```

```

<210> 19
<211> 731
<212> DNA
<213> Homo sapien

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```

<220>
<221> misc_feature
<222> (1)...(731)
<223> n = A,T,C or G

```

```

<400> 19
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gagcccaccg tcacngngng gngtctttat nggagggggc ggagccacat cnetggacnt 120
cntgacccca actccccncc ncnantgca gtgatgagtg cagaactgaa ggtnacgtgg 180
caggaaccaa gancaaannc tgctccntc caagtccgcn nagggggcgg ggctggccac 240
gcncatcctn cnagtgtgn aaagcccn cctgtctact tgtttggaga acngcnnga 300
catgcccagn gttanataac nggcnagag tnannttggc tctccctcc ggetgcgcan 360
cngtntgct tagnggacat aacctgacta cttaactgaa ccnngaate tnccnccct 420
ccactaagct cagaacaaaa aacttcgaca ccactcantt gtcacctgnc tgctcaagta 480
aagtgtaccc catncccaat gntgctnga ngctctgncc tgcnttangt tcggtcctgg 540
gaagacctat caattnaagc tatgtttctg actgcctctt gctccctgna acaancnacc 600
cnnnntcca agggggggnc ggcccccaat ccccccaacc ntnaattnan tttancccn 660
ccccnggcc cggcctttta cnancntcn nnaacnggna aaacnnngc ttncccaac 720

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nnaatccncc t

731

<210> 20  
 <211> 754  
 <212> DNA  
 <213> Homo sapien  
  
 <220>  
 <221> misc\_feature  
 <222> (1)...(754)  
 <223> n = A,T,C or G

<400> 20  
 tttttttttt tttttttttt taaaaacccc ctccattnaa tgnaaacttc cgaaattgtc 60  
 caaccccctc ntccaaatnn ccntttccgg gnggggggtc caaacccaan ttanntttgg 120  
 annttaaatt aaatnttntt tggnggnnna anccnaatgt nangaaagt naaccanta 180  
 tnancttnaa tncctggaaa ccngtngntt ccaaaaatnt ttaaccctta antccctccg 240  
 aaatngttna nggaaaaccc aanttctcnt aaggttggtt gaaggntnaa tnaaaanccc 300  
 nnccaattgt ttttngccac gcctgaatta attggnntcc gntgttttcc nttaaaanaa 360  
 gggnancccc ggttantnaa tcccccnnc cccaattata ccganttttt ttngaattgg 420  
 gancccnccg gaattaacgg ggnnnntccc tnttgggggg cnggnncccc ccccntcggg 480  
 ggttngggnc aggnccnaat tgtttaaggg tccgaaaaat ccctccnaga aaaaaanctc 540  
 ccaggttgag nntnggggtt ncccccccc canggccctc ctcgnanagt tgggggttgg 600  
 ggggcctggg attttntttc ccctnttnc tcccccccc ccnggganag aggttngngt 660  
 tttgntcnnc ggccccnccn aaganccttn ccganttnan ttaaaccnt gcctnggcga 720  
 agtccnttgn agggntaaan ggccccctnn cggg 754

<210> 21  
 <211> 755  
 <212> DNA  
 <213> Homo sapien  
  
 <220>  
 <221> misc\_feature  
 <222> (1)...(755)  
 <223> n = A,T,C or G

<400> 21  
 atcancccat gaccccaaac nngggaccnc tcancgggnc nnnnacnc cgccnatca 60  
 nngtnagnnc actncnnttn natcacnccc cncnactac gcccnanc cnacgccta 120  
 nncanatncc actganngcg cgangtngan ngagaaanct nataccanag ncaccanacn 180  
 ccagctgtcc nanaangect nnnatacngg nnnatccaat ntgnancctc cnaagtattt 240  
 nncnncanat gattttcctn anccgattac ccntncccc tanccctcc cccccaacna 300  
 cgaaggcnct ggnccnaagg nngcgncc cgcctagntc ccnncnaagt cncnnccta 360  
 aactcancn nattaacncc ttcttgagta tcaactcccg aatctcacc tactcaactc 420  
 aaaaanactn gatacaaat aatncaagcc tgnttatnac actntgactg ggtctctatt 480  
 ttagnggtcc ntnaancntc ctaatacttc cagtctnctc tcnccaattt ccnaanggct 540  
 ctttcngaca gcatnttttg gtcccnntt ggggtcttan ngaattgcc ttcntngaac 600  
 gggtcntct tttccttcgg ttancctggm ttcnccggc cagttattat ttcctntttt 660  
 aaattcntnc cntttanttt tggcnttcna aacccccggc cttgaaaacg gccccctgg 720  
 aaaaggttgt tttganaaaa ttttgtttt gttcc 755

<210> 22  
 <211> 849  
 <212> DNA  
 <213> Homo sapien  
  
 <220>

<221> misc\_feature  
 <222> (1)...(849)  
 <223> n = A,T,C or G

<400> 22  
 tttttttttt tttttangtg tngtcgtgca ggtagaggct tactacaant gtgaanacgt 60  
 acgctnggan taangcgacc cganttctag gannccctt aaaatcanac tgtgaagatn 120  
 atcctgnnna cggaanggtc accggnggat nntgctaggg tgncctctcc cannncttn 180  
 cataactcng nggccctgcc caccaccttc ggcgcccnng ngncggggcc cgggtcattn 240  
 gnnttaaccn cactnngcna ncggtttccn nccccnng acccngggga tccggggtn 300  
 tctgtcttcc cctgnagncn anaaantggg ccncgggnccc ctttaccctt nnacaagcca 360  
 cngcctteta nccnngccc cccctccant nngggggact gccnanngt cegttnctng 420  
 nnaccccnmn gggtnccctg gttgtcgant cnaccgnang ccanggatc cnaaggaagg 480  
 tgcgttnttg gcccctaccc ttcgctnccg nncaccttc ccgacnanga nccgtccc 540  
 cncnccgng cctcncctcg caacacccgc nctctcngt nccggnnccc cccacccgc 600  
 nccctcncn ngncgnancn ctccnccnc gtctcannca ccaccccgcc ccgccaggcc 660  
 ntcancacn ggnngacnng nagnccntc gcctccgcn gcgnccct cgcncngaa 720  
 ctntctngg ccantnccgc tcaancnna cnaaacgcc ctgcgcggcc cgnagcgncc 780  
 nccctcncga gtctcccg cttccnacc angnttccn cgaggacacn nnaccccgcc 840  
 nncangcgg 849

<210> 23  
 <211> 872  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(872)  
 <223> n = A,T,C or G

<400> 23  
 gcgcaaaacta tacttcgtc gnaactcgtgc gcctcgtc tcttttctc cgcaaccatg 60  
 tctgacnanc ccgattnggc ngatatcnan aagntcganc agtccaaact gantaacaca 120  
 cacacnncn aganaaatcc nctgccttcc anagtancn attgaacnng agaaccangc 180  
 nggcgaatcg taatnaggcg tgcgcgcgcca atntgtcnc gtttatntn ccagctcnc 240  
 ctncnacc taactcttcn nagctgtcnn accctngtn cgnaccccc naggtcggga 300  
 tcgggtttnn ntggaccgng cncctctcc cccctccat nacgancnc ccgcaccacc 360  
 nanngcncgc ncccggnct ctgcgcnc ctgtctntn cccctgtngc ctggcncngn 420  
 accgcattga cctcgcenn ctncnngaaa ncgnanacgt ccgggttggn annancgtg 480  
 tgggnngcg tctgncgc gtctctccn ncncttcca ccatcttnt tacnggtct 540  
 ccnccctc tcnncacnc cctgggagc tntctntgc ccccttnac tccccctt 600  
 cgnctgncc cgncccccacc ntcatttnca nacgntctt acaannccct ggntnnctcc 660  
 cnancngncn gtcancnag ggaagggngg ggnccnntg nttgacgttg ngngangtc 720  
 cgaanantcc tcnctcan cctaccct cggcggnct ctngttncc aacttancaa 780  
 ntctccccg ngngcncntc tcagctcnc cncccnct ctctgcantg tntctgctc 840  
 tnaccntac gantnttcgn cncctctt cc 872

<210> 24  
 <211> 815  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(815)  
 <223> n = A,T,C or G



&lt;400&gt; 24

gcatgcaagc	ttgagtattc	tatagngtca	cctaaatanc	ttggcntaat	catggtcnta	60
nctgncttcc	tgtgtcaa	gtatacna	tanatatgaa	tctnatntga	caaganngt	120
tcntncatta	gtaacaantg	tnntgtccat	cctgtcngan	canattccca	tnnattncgn	180
cgcattcn	gncantatn	taatngggaa	ntcnntnnn	ncaccnncat	ctatcntncc	240
gncccctgac	tggagagat	ggatnanttc	tnntntgacc	nacatgttca	tcttggattn	300
aanancccc	cgcngnccac	cggttngnng	cnagccnntc	ccaagacctc	ctgtggaggt	360
aacctgcgtc	aganncatca	aacntgggaa	acccgcnncc	angtnnaagt	ngnnncanan	420
gatcccgccc	aggnttnacc	atcccttcnc	agcgccccct	ttngtgcctt	anagnnagc	480
gtgtccnanc	cnctcaacat	ganacgcgcc	agnccanccg	caattnggca	caatgtcgnc	540
gaaccccccta	gggggantna	tncaaanccc	caggattgtc	cncncangaa	atcccnanc	600
ccnccctac	ccncttttg	gacngtgacc	aantcccgga	gtncagtc	ggccngnctc	660
ccccaccggt	nnccntgggg	gggtgaanct	cngnntcanc	cngncgaggn	ntcgnaagga	720
accggncctn	ggncgaanng	ancnntcnga	agnccnct	cgtataacc	cccctcncca	780
nccnacngnt	agntcccccc	cngggtncgg	aangg			815

&lt;210&gt; 25

&lt;211&gt; 775

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(775)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 25

ccgagatgtc	tgcgtccgtg	gccttagctg	tgctcgcgct	actctctctt	tctggcctgg	60
aggctatcca	gcgtactcca	aagattcagg	tttactcacg	tcacccagca	gagaatggaa	120
agtcaaattt	cctgaattgc	tatgtgtctg	ggtttcatcc	atccgacatt	gaanttact	180
tactgaagaa	tgganagaga	attgaaaaag	tggagcattc	agacttgtct	ttcagcaagg	240
actgggtctt	ctatctcntg	tactacactg	aattcacccc	cactgaaaaa	gatgagtatg	300
cctgccgtgt	gaaccatgtg	actttgtcac	agcccaagat	agttaagtgg	gatcgagaca	360
tgtaagcagn	cnncatggaa	gtttgaagat	gccgcatttg	gattggatga	attccaaatt	420
ctgcttgctt	gcntttta	antgatatgc	ntatacaccc	taccctttat	gnccccaat	480
tgtagggtt	acatnantgt	tcnctntnga	catgatcttc	ctttataant	ccnccnttcg	540
aattgcccg	cnccngttn	ngaattgttc	cnaaccacg	gttggtccc	ccaggtcncc	600
tcttacggaa	gggectgggc	cncctttncaa	ggttggggga	accnaaaatt	tcnctntgc	660
ccncccncca	cnntcttng	nnncanttt	ggaacccttc	cnattccct	tggcctcna	720
nccttnncta	anaaaacttn	aaancgtngc	naaanntttn	acttcccccc	ttacc	775

&lt;210&gt; 26

&lt;211&gt; 820

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(820)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 26

anattantac	agtgtaatct	tttcccagag	gtgtgtanag	ggaacggggc	ctagaggcat	60
cccanagata	ncttatanca	acagtgtctt	gaccaagagc	tgtgtggcac	atttcctgca	120
gaaaaggtgg	cggctcccat	cactcctcct	ctcccatagc	catcccagag	gggtgagtag	180
ccatcangcc	ttcggtggga	gggagtcang	gaaacaacan	accacagagc	anacagacca	240
ntgatgacca	tgggcggggg	cgagcctctt	ccctgnaccg	gggtggcana	nganagccta	300
nctgaggggt	cacactataa	acgttaacga	ccnagatnan	cacctgtctc	aagtgacccc	360

ttcctacctg	acnaccagng	accnnnaact	gcngcctggg	gacagcnetg	ggancagcta	420
acnnagcact	cacctgcccc	cccatggccg	tncgntccc	tggtcctgnc	aagggaagct	480
ccctgttgga	attncgggga	naccaaggga	nccccctcct	ccanctgtga	aggaaaaann	540
gatggaattt	tncccttccg	gccnntcccc	tcttccttta	cacgccccct	nntactcntc	600
tccctctntt	ntcctgncnc	acttttnacc	ccnnnatctc	ccttnattga	tcggannctn	660
ganattccac	tnnccgctnc	cntcnatcng	naanacnaaa	nactntctna	ccnnggggat	720
gggnncctcg	ntcatcctct	ctttttcnct	accnccnntt	ctttgcctct	ccttngatca	780
tccaacntc	gntggccntn	ccccccnnt	tcctttnccc			820

&lt;210&gt; 27

&lt;211&gt; 818

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(818)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 27

tctgggtgat	ggcctcttcc	tcctcagggg	cctctgactg	ctctgggcca	aagaatctct	60
tgtttcttct	ccgagcccca	ggcagcgggt	attcagccct	gcccacactg	attctgatga	120
ctgcggatgc	tgtgacggac	ccaaggggca	aatagggtcc	cagggtccag	ggaggggcgc	180
ctgctgagca	cttcgcgccc	tcacctgcc	cagccctgc	catgagctct	gggctgggtc	240
tccgcctcca	gggttctgct	cttccangca	ngccancaag	tggcgctggg	ccacactggc	300
ttcttctgct	ccntccctg	gctctganc	tctgtcttcc	tgctctgtgc	angcnccttg	360
gatctcagtt	tccctcnctc	anngaactct	gtttctgann	tcttcantta	actntgantt	420
tatnaccnan	tggnctgtnc	tgtnnactt	taatgggcn	gaccggctaa	tcctccctc	480
ntcccttcc	anttcnnna	accngcttnc	cntctctcc	ccntancccg	ccnggggaanc	540
ctcctttgcc	ctnaccang	gccnnnaccg	ccntnnctn	ggggggcnng	gtnnctnenc	600
ctgntnnccc	cnctcnctn	tnctcgtcc	cnnccnccn	nnccancttc	ncngtcccn	660
tnnctcttcc	ngntctgnaa	ngntcnctn	tnnnnngncc	ngntnntncc	tcctctcnc	720
cnnntgnang	tnnttnnncc	ncngnncccc	nnnnnnnnnn	nggnnnntnn	tctnccngc	780
ccnncccccc	ngnattaagg	cctccnctct	ccggccnc			818

&lt;210&gt; 28

&lt;211&gt; 731

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(731)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 28

aggaagggcg	gagggatatt	gtangggatt	gagggatagg	agnataangg	gggaggtgtg	60
tccaacatg	anggtgnngt	tctcttttga	angaggggtg	ngtttttann	ccnggtgggt	120
gattnaaccc	cattgtatgg	agmnaaaggn	tttnagggat	ttttcggtct	ttatcagtat	180
ntanattcct	gtnaatcgga	aaatnatntt	tcnnccggaa	aatnttgctc	ccatccgnaa	240
attnctcccg	ggtagtgc	nttngggggn	cngccangtt	tcccaggctg	ctanaatcgt	300
actaaagntt	naagtggan	tncaaatgaa	aacctnncc	agagnatccn	taccgcactg	360
tnnnntnct	tcgcccctng	actctgcng	agcccaatac	ccnngngnat	gtcncccngn	420
nnngcgnenc	tgaaannnnc	tcngggctnn	gancatcang	gggtttcgca	tcaaaagcnn	480
cgtttcncat	naaggcactt	tngectcatc	caaccnctng	ccctcnncca	tttngccgtc	540
nggttcnct	acgetnntng	cncctnnntn	ganattttnc	ccgcctnggg	naancctcct	600
gnaatgggta	gggncttntc	ttttnacnnc	gnggtntact	aatcnnctnc	acgcntnctt	660
tctcnacccc	cccccttttt	caatcccanc	ggcnaatggg	gtctccccnn	cgangggggg	720

nnncccannc c

731

<210> 29  
 <211> 822  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(822)  
 <223> n = A,T,C or G

<400> 29  
 actagtccag tgtggtggaa ttccattgtg ttggggncnc ttctatgant antnttagat 60  
 cgctcanacc tcacancctc ccnacnangc ctataangaa nannaataga nctgtncnnt 120  
 atntntacnc tcatanncct cnnnaccac tccctcttaa cccntactgt gcctatngcn 180  
 tnnctantct ntgcgcctn cnanccaccn gtgggcnac cncnngnatt ctcnatctcc 240  
 tcncctatntn gcctananta ngtncatacc ctatacctac nccaatgcta nnnctaancn 300  
 tccatnantt annntaacta ccaactgaent ngactttcnc atnanctcct aatttgaatc 360  
 tactctgact cccacngcct annnattagc ancntcccc nacnatntct caaccaaatc 420  
 ntcaacaacc tatctantctg ttcnccaacc nttncctcgc atccccnnac aacccccctc 480  
 ccaaataccc nccacctgac ncctaaccen caccatcccg gcaagccnan ggncatttan 540  
 ccactggaat cacnatngga naaaaaaac ccnaactctc tancncnnat ctccctaana 600  
 aatnctcctn naatttactn ncantnccat caanccacn tgaaacnnaa cccctgtttt 660  
 tanatccctt ctttcgaaaa ccnacccttt annncccaac ctttngggcc ccccnctnc 720  
 ccnaatgaag gncnccaat cnangaaacg nccntgaaaa ancnaggcna anannntccg 780  
 canatcctat cccttanttn ggggnccctt nccnngggcc cc 822

<210> 30  
 <211> 787  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(787)  
 <223> n = A,T,C or G

<400> 30  
 cggcgcctg ctctggcaca tgctcctga atggcatcaa aagtgatgga ctgcccattg 60  
 ctagagaaga ccttctctcc tactgtcatt atggagccct gcagactgag ggctcccctt 120  
 gtctgcagga tttgatgtct gaagtgcgtg agtggtgctt ggagctcctc atctacatna 180  
 gctggaagcc ctggagggcc tctctcgcca gcctccccct tctctccacg ctctccangg 240  
 acaccagggg ctccaggcag cccattattc ccagnangac atggtgtttc tccacgcgga 300  
 cccatggggc ctgnaaggcc aggtgtcctt ttgacaccat ctctccgctc ctgcttgcca 360  
 ggccgtggga tccactantt ctanaacggg cgccaccncc gtgggagctc cagcttttgt 420  
 tcccnttaat gaaggttaat tgencgcttg gcgtaatcat nggtcanaac tntttctgt 480  
 gtgaaattgt tnttccccct ncnattccnc ncnacatacn aacccggaan cataaagtgt 540  
 taaagcctgg gggtnccctn nngaataaac tnaactcaat taattgcgtt ggctcatggc 600  
 ccgctttccn ttcnngaaaa ctgtentccc ctgenttntt gaatcggeca ccccccnggg 660  
 aaaagcggtt tgcnttttng ggggntcctt ccncttcccc cctcnctaan cctnccgct 720  
 cggtcgttnc nggtngcggg gaangggnat nnnctccnc naagggggng agnnngntat 780  
 ccccaaa 787

<210> 31  
 <211> 799  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(799)  
 <223> n = A,T,C or G

<400> 31  
 tttttttttt tttttttggc gatgctactg ttttaattgca ggaggtgggg gtgtgtgtac 60  
 catgtaccag ggctattaga agcaagaagg aaggagggag ggagagcgc cctgctgagc 120  
 aacaaaggac tcctgcagcc ttctctgtct gtctcttggc gcaggcacat ggggaggcct 180  
 cccgcagggt gggggccacc agtccagggt tgggagcact acanggggtg ggagtgggtg 240  
 gtggctggtg cnaatggcct gncacanatc cctacgattc ttgacacctg gatttcacca 300  
 ggggaccttc tgttctccca nggnaacttc nttnatctcn aaagaacaca actgtttctt 360  
 cngcanttct ggctgttcat ggaaagcaca ggtgtccnat ttnggctggg acttgggtaca 420  
 tatggttccg gcccacctct cccntcnaaa aagtaattca ccccccccn cctctnttg 480  
 cctgggccct taantaccca caccggaact canttantta ttcactctng gntgggcttg 540  
 ntnatcnccn cctgaangcg ccaagttgaa aggccacgcc gtncccnctc cccatagnan 600  
 nttttnnct canctaagtc cccccnnggc aacnatccaa tcccccccn tgggggcccc 660  
 agcccanggc ccccgctcgc ggnnccngn cncgnantcc ccaggtctc ccantcngnc 720  
 ccnnngcncc cccgcacgca gaacanaagg ntngagcnc cgcannnnnn nggttnncac 780  
 ctgcccccc cccnngnng 799

<210> 32  
 <211> 789  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(789)  
 <223> n = A,T,C or G

<400> 32  
 tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt tttttttttt 60  
 ttttnccnag ggcaggttta ttgacaacct cncgggacac aancaggctg gggacaggac 120  
 ggcaacaggc tccggcggcg gcggcggcg ccctacctgc ggtaccaaata ntgcagcctc 180  
 cgctcccgtc tgatnttct ctgcagctgc aggatgccnt aaaacagggc ctccggcctn 240  
 ggtggggcacc ctgggatttn aatttccacg ggcacaatgc ggtcgcancc cctcaccacc 300  
 nattaggaat agtggtnnta cccnccnccg ttggcncact ccccntggaa accactntc 360  
 gcggtcccg catctggtct taaaccttgc aaacnctggg gccctctttt tggttantnt 420  
 nccngccaca atcatnactc agactggcnc gggctggccc caaaaaancn ccccaaaacc 480  
 ggnccatgtc ttncgggggt tgetgcnatn tncatcacct cccgggcnca ncaggncaac 540  
 ccaaaagtgc ttngggcccn caaaaaanct cgggggggnc ccagtttcaa caaagtcac 600  
 ccccttggcc cccaaatcct ccccccgnt nctgggttg ggaaccacg cctctnnctt 660  
 tggngggcaa gntggntccc ccttcgggcc cccggtgggc ccnctctaa ngaaaacncc 720  
 ntccnnnca ccatcccccc nngnnacgnc tancaangna tccctttttt tanaaacggg 780  
 cccccnccg 789

<210> 33  
 <211> 793  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(793)  
 <223> n = A,T,C or G

&lt;400&gt; 33

gacagaacat	gttggatggt	ggagcacctt	tctatacgac	ttacaggaca	gcagatgggg	60
aattcatggc	tggttgagca	atanaacccc	agttctacga	gctgctgac	aaaggacttg	120
gactaaagtc	tgatgaactt	cccaatcaga	tgagcatgga	tgattggcca	gaaatgaana	180
agaagtttgc	agatgtatth	gcaaagaaga	cgaaggcaga	gtggtgtcaa	atctttgacg	240
gcacagatgc	ctgtgtgact	ccggttctga	cttttgagga	ggttgttcat	catgatcaca	300
acaangaacg	gggtcgttt	atcaccantg	aggagcagga	cgtgagcccc	cgccctgcac	360
ctctgctgtt	aaacacccca	gccatccctt	ctttcaaaag	ggatccacta	cttctagagc	420
ggncgccacc	gcggtggagc	tccagctttt	gttcccttta	gtgagggtta	attgcgcgct	480
tgcgtaatc	atggtcatan	ctgtttcctg	tgtgaaattg	ttatccgctc	acaattccac	540
acaacatacg	anccggaagc	atnaaatttt	aaagcctggg	ggtngcctaa	tgantgaact	600
nactcacatt	aattggcttt	gcgtcactg	cccgttttcc	agtccggaaa	acctgtcctt	660
gccagctgcc	nttaatgaat	cnggccaccc	cccggggaaa	aggcngtttg	cttnttgggg	720
cgccttccc	gctttctcgc	ttcctgaant	ccttccccc	ggtctttcgg	cttgccgcna	780
acggtatcna	cct					793

&lt;210&gt; 34

&lt;211&gt; 756

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)... (756)

&lt;223&gt; n = A, T, C or G

&lt;400&gt; 34

gccgcgaccg	gcatgtacga	gcaactcaag	ggcgagtggg	accgtaaaag	ccccaatctt	60
ancaagtgcg	gggaanagct	gggtcgactc	aagctagttc	ttctggagct	caacttcttg	120
ccaaccacag	ggaccaagct	gaccaaacag	cagctaattc	tggcccgtga	catactggag	180
atcggggccc	aatggagcat	cctacgcaan	gacatccctt	ccttcgagcg	ctacatggcc	240
cagctcaaat	gctactactt	tgattacaan	gagcagctcc	ccgagtcagc	ctatatgcac	300
cagctcttgg	gcctcaacct	cctcttcttg	ctgtcccaga	accgggtggc	tgantnccac	360
acgganttgg	ancggctgcc	tgcccanga	catacanacc	aatgtctaca	tcnaccacca	420
gtgtcctgga	gcaatactga	tgganggcag	ctaccncaaa	gtnttccctg	ccnagggtaa	480
catccccgcg	cgagagctac	accttcttca	ttgacatcct	gctcgacact	atcagggatg	540
aaaatcgong	ggttgctcca	gaaaggctnc	aanaanatcc	ttttcncctg	aggcccccgg	600
atncnctagt	ncagaatcg	gcccgccatc	gcggtgganc	ctccaacctt	tcgttnccct	660
ttactgaggg	tttattgccg	cccttggcgt	tatcatggtc	acnccngttt	cctgtgttga	720
aattnttaac	ccccacacat	tccacgcena	catting			756

&lt;210&gt; 35

&lt;211&gt; 834

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)... (834)

&lt;223&gt; n = A, T, C or G

&lt;400&gt; 35

ggggatctct	anatonacct	gnatgcatgg	ttgtcgggtg	ggtcgctgtc	gatgaanatg	60
aacaggatct	tgcccttgaa	gctctcggtt	gctgtnttta	agttgctcag	tctgccgtca	120
tagtcagaca	cncctctggg	caaaaaacan	caggatntga	gtcttgattt	cacctccaat	180
aatcttongg	gctgtctgct	cggtgaactc	gatgacnang	ggcagctggg	tgtgtntgat	240
aaantccanc	angttctcct	tggtgacctc	cccttcaaag	ttgttccggc	cttcatcaaa	300
cttctnnaan	angannancc	canctttgtc	gagctggnat	ttgganaaca	cgtcactgtt	360

ggaaactgat	cccaaattgt	atgtcatcca	tgcctctgc	tgcctgcaa	aaacttgctt	420
ggcncaaatac	cgactcccn	tccttgaaag	aagccnatca	cacccccctc	cctggactcc	480
nncaangact	ctnccgctnc	ccntccnng	cagggttggt	ggcannccgg	gccntgcgc	540
ttcttcagcc	agttcacnat	nttcacagc	ccctctgcc	gctgtntat	tccttggggg	600
ggaanccgtc	tctcccttcc	tgaannaact	ttgaccgtng	gaatagccgc	gcntcnccnt	660
acntnctggg	ccgggttcaa	antccctccn	ttgncnntcn	cctcgggcc	ttctggattt	720
nccnaacttt	ttccttcccc	cncnccnccg	ngtttgntt	tttcatnggg	ccccaactct	780
gctnttgcc	antccctgg	gggcntntan	cncnccctnt	ggtccentng	ggcc	834

<210> 36  
 <211> 814  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)... (814)  
 <223> n = A,T,C or G

<400> 36						
cgngcgcttt	ccngccgcgc	cccgtttcca	tgacnaaggc	tcccttcang	ttaaatacnn	60
cctagnaaac	attaatgggt	tgtctacta	atacatcata	cnaaccagta	agcctgcccc	120
naacgccaac	tcaggccatt	cctaccaaag	gaagaaaggc	tggtctctcc	accccctgta	180
ggaaaggcct	gccttgtaag	acaccacaat	ncggtgaat	ctnaagtctt	gtgttttact	240
aatggaaaaa	aaaaataaac	aanaggtttt	gttctcatgg	ctgcccaccg	cagcctggca	300
ctaaaacanc	ccagcgctca	cttctgcttg	ganaaatatt	ctttgctctt	ttggacatca	360
ggcttgatgg	tatcactgcc	acntttccac	ccagctgggc	ncccttcccc	catntttgtc	420
antganctgg	aaggcctgaa	ncttagtctc	caaaagtctc	ngcccacaag	accggccacc	480
aggggagntc	ntttncagtg	gatctgccaa	anantaccn	tatcatcnnt	gaataaaaag	540
gcccctgaac	ganatgcttc	cancancett	taagaccat	aatcctngaa	ccatgggtgcc	600
cttcgggtct	gatccnaaag	gaatgttct	gggtcccant	ccctcctttg	ttncctacgt	660
tgtnttgac	ccntgctngn	atnaccnaan	tganaatccc	ngaagcacc	tnccctggc	720
atgtganttt	cntaaattct	ctgcctacn	nctgaaagca	cnattccctn	ggcncnaaan	780
gnggaactca	agaaggtctn	ngaaaaacca	cncn			814

<210> 37  
 <211> 760  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)... (760)  
 <223> n = A,T,C or G

<400> 37						
gcatgctgct	cttctcctcaa	gttggtcttg	ttgccataac	aaccaccata	ggtaaagcgg	60
gcgcagtggt	cgctgaagg	gttgtagtac	cagcgcgga	tgctctcctt	gcagagtctt	120
gtgtctggca	ggctccagca	atgcccttg	tactgggga	aatggatgcg	ctggagctcg	180
tcnaanccac	tcgtgtattt	ttcacangca	gcctcctccg	aagctccgg	gcagttgggg	240
gtgtcgtcac	actccactaa	actgtcgatn	cancagccca	ttgctgcagc	ggaactgggt	300
gggctgacag	gtgccagaac	acactggatn	ggcctttcca	tggaaaggcc	tgggggaaat	360
cncctnancc	caaaactgcct	ctcaaaggcc	accttgacac	ccccgacagg	ctagaaatgc	420
actcttcttc	ccaaaggtag	ttgttcttgc	tgcccaagca	ncctccanca	aaccaaaanc	480
ttgcaaaatc	tgctccgtgg	gggtcatnnn	taccanggtt	ggggaaanaa	acccggcngn	540
ganccnccct	gtttgaatgc	naaggnaata	atcctcctgt	cttgcttggg	tggaaanagca	600
caattgaact	gttaacnttg	ggccnggttc	cncnnggtg	gtctgaaact	aatcacgcgc	660
actggaaaaa	ggtangtgcc	ttccttgaat	tcccaaantt	cccctngntt	tgggtntttt	720

ctcctctncc ctaaaaatcg tnttcccccc ccntanggcg

760

<210> 38  
 <211> 724  
 <212> DNA  
 <213> Homo sapien  
 <220>  
 <221> misc\_feature  
 <222> (1)...(724)  
 <223> n = A,T,C or G

<400> 38  
 tttttttttt tttttttttt tttttttttt tttttaaaaa cccctcccat tgaatgaaaa 60  
 cttccnaaat tgtccaaccc cctcnnccaa atnnccattt ccgggggggg gttccaaacc 120  
 caaattaatt ttgganttta aattaaatnt tnattngggg aanaanccaa atgtnaagaa 180  
 aatttaaccc attatnaact taaatnccn gaaaccntg gnttccaaaa atttttaacc 240  
 cttaaatccc tccgaaattg ntaanggaaa accaaattcn cctaaggctn tttgaagggt 300  
 ngatttaaac ccccttnant tnttttnacc cnnngctnaa ntatttngnt tccggtgttt 360  
 tcctnttaan cntnggtaac tcccngtaat gaannnccct aanccaatta aaccgaattt 420  
 tttttgaatt ggaaattccn ngggaattna ccgggggttt tcccttttgg ggcccatncc 480  
 cccnctttcg gggtttgggn ntaggttgaa tttttnnang ncccaaaaaa ncccccaana 540  
 aaaaaactcc caagnnttaa ttngaattnc ccccttccca ggccttttgg gaaaggnggg 600  
 tttntggggg ccngggantt cnttcccccn ttncncccc ccccccnggt aaanggttat 660  
 ngnttttggg ttttgggcc cttnanggac cttccggatn gaaattaaat ccccggnncg 720  
 gccg 724

<210> 39  
 <211> 751  
 <212> DNA  
 <213> Homo sapien  
 <220>  
 <221> misc\_feature  
 <222> (1)...(751)  
 <223> n = A,T,C or G

<400> 39  
 tttttttttt tttttctttg ctcacattta atttttattt tgattttttt taatgctgca 60  
 caacacaata tttatttcat ttgtttcttt tatttcattt tatttgttg ctgctgctgt 120  
 tttatttatt tttactgaaa gtgagaggga acttttgttg ccttttttcc tttttctgta 180  
 ggccgcctta agcttttctaa atttggaaca tctaagcaag ctgaanggaa aagggggttt 240  
 cgcaaaatca ctcgggggaa nggaaagggt gctttgttaa tcatgcccta tgggtgggtga 300  
 ttaactgctt gtacaattac ntttcacttt taattaattg tgctnaangc ttttaattana 360  
 cttgggggtt cctccccan accaaccn ctgacaaaaa gtgccngccc tcaaatnatg 420  
 tcccggcnnt cnttgaaaca cacngcngaa ngttctcatt ntccccncnc caggtnaaaa 480  
 tgaagggtta ccatntttaa cnccacctcc acntggcnnn gcctgaatcc tcnaaaancn 540  
 ccctcaancn aattnctnng ccccggtcnc gcntnngtcc cncgcgggct ccgggaantn 600  
 cacccccnga anncnntnnc naacnaaatt ccgaaaatat tcccnntcnc tcaattcccc 660  
 cnnagactnt cctcnnncn cncaattttc ttttnntcac gaacnngnnc cnnaaatgn 720  
 nnnncnctc cnctngtcn naatcnccan c 751

<210> 40  
 <211> 753  
 <212> DNA  
 <213> Homo sapien

<220>

<221> misc\_feature  
 <222> (1)...(753)  
 <223> n = A,T,C or G

<400> 40  
 gtggtatttt ctgtaagatc aggtgtttcct ccctcgtagg tttagaggaa acaccctcat 60  
 agatgaaaac cccccgaga cagcagcact gcaactgcca agcagccggg gtaggagggg 120  
 cgccctatgc acagctgggc ccttgagaca gcagggttc gatgtcaggc tcgatgtcaa 180  
 tggctctgaa gcggcggtg tacctgcgta ggggcacacc gtcagggcc accaggaact 240  
 tctcaaagtt ccaggcaacn tcgttgcgac acaccggaga ccagggtatn agcttggggg 300  
 cggtcataan cgcggtggcg tcgtcgctgg gagctggcag ggcctccgc aggaaggcna 360  
 ataaaaggtg cgccccgca cggttcanct cgcacttctc naanaccatg angttgggct 420  
 cnaaccacc accannccgg acttcttga nggaattccc aaatctcttc gntcttgggc 480  
 ttctnctgat gccctanctg gttgccnngn atgccaanca nccccaancc cgggggtcct 540  
 aaanaccn cctcctcctt tcatctgggt tntntcccc ggacctgtgt tcctctcaag 600  
 gganccata tctcnaccan tactcaccnt ncccccent gnnaccanc cttctanngn 660  
 ttccncccg ncctctggcc cntcaaan gcttnacna cctgggtctg ccttcccccc 720  
 tnccctatct gnaccnncn tttgtctcan tnt 753

<210> 41  
 <211> 341  
 <212> DNA  
 <213> Homo sapien

<400> 41  
 actatatcca tcacaacaga catgtttcat cccatagact tcttgacata gttcaaagt 60  
 agtgaacca tccttgattt atatacatat atgttctcag tttttggga gcctttccac 120  
 ttctttaaac cttgttcatt atgaacactg aaaataggaa tttgtgaaga gttaaaaagt 180  
 tatagcttgt ttacgtagta agtttttgaa gtctacattc aatccagaca cttagttagg 240  
 tgttaaactg tgatttttaa aaaatatcat ttgagaatat tctttcagag gtattttcat 300  
 ttttactttt tgattaattg tgttttatat attagggtag t 341

<210> 42  
 <211> 101  
 <212> DNA  
 <213> Homo sapien

<400> 42  
 acttactgaa tttagtcttg tgctcttcct tatttagtgt tgtatcataa atactttgat 60  
 gtttcaaaca ttctaaataa ataattttca gtggcttcat a 101

<210> 43  
 <211> 305  
 <212> DNA  
 <213> Homo sapien

<400> 43  
 acatctttgt tacagtctaa gatgtgttct taaatcacca ttccttcctg gtctcacc 60  
 tccagggtgg tctcactg taattagagc tattgaggag tctttacagc aaatttagat 120  
 tcagatgcct tgctaagtct agagttctag agttatgttt cagaaagtct aagaaacca 180  
 cctcttgaga ggtcagtaaa gaggacttaa tatttcatat ctacaaaatg accacaggat 240  
 tggatacaga acgagagtta tcttgataa ctcagagctg agtacctgcc cgggggccc 300  
 tcgaa 305

<210> 44  
 <211> 852  
 <212> DNA  
 <213> Homo sapien



<220>  
 <221> misc\_feature  
 <222> (1)...(852)  
 <223> n = A,T,C or G

<400> 44  
 acataaatat cagagaaaag tagtctttga aatatttacg tccaggagtt ctttgtttct 60  
 gattatttgg tgtgtgtttt ggtttgtgtc caaagtattg gcagcttcag ttttcatttt 120  
 ctctccatcc tcgggcattc ttcccaaatt tatataccag tcttcgtcca tccacacgct 180  
 ccagaatttc tctttttag tagtatctca tagctcggct gagcttttca taggtcatgc 240  
 tgctggtgtt cttcttttta ccccatagct gagccactgc ctctgatttc aagaacctga 300  
 agacgccctc agatcgggtct tcccatttta ttaatcctgg gttcttgtct gggttcaaga 360  
 ggatgtcggc gatgaattcc cataagttag tccctctcgg gttgtgcttt ttggtgtggc 420  
 acttggcagg ggggtcttgc tcctttttca tatcaggtag ctctgcaaca ggaaggtgac 480  
 tggtaggtgt catggagatc tgagcccgcc agaaagtatt gctgtccaac aaatctactg 540  
 tgctaccata gttggtgtca tataaatagt tctngtcttt ccagggtgtc atgatggaag 600  
 gctcagtttg ttcagtcttg acaatgacat tgtgtgtgga ctggaacagg tcactactgc 660  
 actggccgtt ccacttcaga tgcgtcaagt tgctgtagag gagntgccc gccgtccctg 720  
 ccgccgggt gaactcctgc aaactcatgc tgcaaaggtg ctgcgcgttg atgtcgaaact 780  
 cntggaaagg gatacaattg gcatccagct ggtaggtgtc caggaggtga tggagccact 840  
 cccacacctg gt 852

<210> 45  
 <211> 234  
 <212> DNA  
 <213> Homo sapien

<400> 45  
 aacacagacc cttgctcgtc aacgacctca tgctcatcaa gttggacgaa tccgtgtccg 60  
 agtctgacac catccggagc atcagcattg cttcgcagtg ccctaccgcg gggaactctt 120  
 gcctcgtttc tggtcggggc ctgctggcga acggcagaat gcctaccgtg ctgcagtgcg 180  
 tgaacgtgtc ggtggtgtct gaggaggtct gcagtaagct ctatgaccgc ctgt 234

<210> 46  
 <211> 590  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(590)  
 <223> n = A,T,C or G

<400> 46  
 actttttatt taaatgttta taaggcagat ctatgagaat gatagaaaac atggtgtgta 60  
 atttgatagc aatatttttg agattacaga gtttttagtaa ttaccaatta cacagttaaa 120  
 aagaagataa tatattccaa gcanatacaa aatatctaata gaaagatcaa ggcaggaaaa 180  
 tgantataac taattgacaa tggaaaatca attttaatgt gaattgcaca ttatccttta 240  
 aaagctttca aaanaaanaa ttattgcagt ctanttaatt caaacagtgt taaatggtat 300  
 caggataaan aactgaagg gnaaaagaat taattttcac ttcagttaac ncacccanac 360  
 ttacaatggc ttaaattgcan ggaaaaagca gtggaagttag ggaagtantc aaggtctttc 420  
 tggctctctaa tctgccttac tctttgggtg tggttttgat cctctggaga cagctgccag 480  
 ggctcctgtt atatccacaa tcccagcagc aagatgaagg gatgaaaaag gacacatgct 540  
 gccttccttt gaggagactt catctcactg gccaacactc agtcacatgt 590

<210> 47  
 <211> 774

<212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(774)  
 <223> n = A,T,C or G

<400> 47  
 acaagggggc ataatgaagg agtggggana gattttaaag aaggaaaaaa aacgaggccc 60  
 tgaacagaat ttctctgnac aacggggcctt caaaataatt ttcttgggga ggttcaagac 120  
 gcttcactgc ttgaaactta aatggatgtg ggacanaatt ttctgtaatg accctgaggg 180  
 cattacagac gggactctgg gaggaaggat aaacagaaag gggacaaagg ctaatcccaa 240  
 aacatcaaag aaaggaaggt ggcgtcatat ctcccagcct acacagttct ccagggtctt 300  
 cctcatccct ggaggacgac agtggaggaa caactgacca tgtccccagg ctccctgtgtg 360  
 ctggctcctg gtcttcagcc cccagctctg gaagcccacc ctctgtctgat cctgcgtggc 420  
 ccacactcct tgaacacaca tcccaggtt atattcctgg acatggctga acctcctatt 480  
 cctacttccg agatgccttg ctccctgcag cctgtcaaaa tcccactcac cctccaaacc 540  
 acggcatggg aagcctttct gacttgcttg attactccag catcttgaa caatccctga 600  
 ttcccactc cttagaggca agatagggtg gtttaagagta gggctggacc acttgagacc 660  
 aggctgctgg cttcaaattt tggctcattt acgagctatg ggaccttggg caagtnatct 720  
 tcacttctat gggcntcatt ttgttctacc tgcaaaatgg gggataataa tagt 774

<210> 48  
 <211> 124  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(124)  
 <223> n = A,T,C or G

<400> 48  
 canaaattga aattttataa aaaggcattt ttctcttata tccataaaat gatataattt 60  
 ttgcaantat anaaatgtgt cataaattat aatgttctt aattacagct caacgcaact 120  
 tggt 124

<210> 49  
 <211> 147  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(147)  
 <223> n = A,T,C or G

<400> 49  
 gcogatgcta ctattttatt gcaggaggtg ggggtgtttt tattattctc tcaacagctt 60  
 tgtggctaca ggtggtgtct gactgcatna aaaanttttt tacgggtgat tgcaaaaatt 120  
 ttagggcacc catatcccaa gcantgt 147

<210> 50  
 <211> 107  
 <212> DNA  
 <213> Homo sapien

<400> 50  
 acattaaatt aataaaagga ctgttggggt tctgctaaaa cacatggctt gatataattgc 60  
 atggtttgag gttaggagga gttaggcata tgttttggga gagggggt 107

<210> 51  
 <211> 204  
 <212> DNA  
 <213> Homo sapien

<400> 51  
 gtcctaggaa gtctagggga cacacgactc tggggtcacg gggccgacac acttgcacgg 60  
 cgggaaggaa aggcagagaa gtgacaccgt cagggggaaa tgacagaaag gaaaatcaag 120  
 gccttgcaag gtcagaaagg ggactcaggg cttccaccac agccctgccc cacttggcca 180  
 cctccctttt gggaccagca atgt 204

<210> 52  
 <211> 491  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(491)  
 <223> n = A,T,C or G

<400> 52  
 acaaagataa catttatctt ataacaaaaa tttgatagtt ttaaagggtta gtattgtgta 60  
 gggatatttc caaaagacta aagagataac tcaggtaaaa agttagaaat gtataaaaca 120  
 ccatcagaca ggttttttaa aaacaacata ttacaaaatt agacaatcat ccttaaaaaa 180  
 aaaacttctt gtatcaattt cttttgttca aaatgactga ctttaantatt tttaaatatt 240  
 tcanaaacac ttcctcaaaa attttcaana tggtagcttt canatgtgcc ctcagtcca 300  
 atgttgctca gataaataaa tctcgtgaga acttaccacc caccacaagc tttctggggc 360  
 atgcaacagt gtcttttctt tnccttttct tttttttttt ttacaggcac agaaactcat 420  
 caattttatt tggataacaa aggtgtctca aattatattg aaaaataaat ccaagttaat 480  
 atcactcttg t 491

<210> 53  
 <211> 484  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(484)  
 <223> n = A,T,C or G

<400> 53  
 acataattta gcagggctaa ttaccataag atgctattta ttaanaggtn tatgatctga 60  
 gtattaacag ttgctgaagt ttggtatttt tatgcagcat tttctttttg ctttgataac 120  
 actacagaac ccttaaggac actgaaaatt agtaagtaaa gttcagaaac attagctgct 180  
 caatcaaate tctacataac actatagtaa ttaaaacgtt aaaaaaaagt gttgaaatct 240  
 gcactagtat anaccgctcc tgtcaggata anactgcttt ggaacagaaa gggaaaaanc 300  
 agctttgant ttctttgtgc tgatangagg aaaggctgaa ttaccttggt gcctctccct 360  
 aatgattggc aggtcnggta aatnccaaaa catattccaa ctcaacactt cttttccncg 420  
 tancttgant ctgtgtattc caggancagg cggatggaat gggccagccc ncggatgttc 480  
 cant 484

<210> 54

<211> 151  
 <212> DNA  
 <213> Homo sapien

<400> 54  
 actaaacctc gtgcttga actccatata gaaaacgggtg ccatccctga acacggctgg 60  
 ccactgggta tactgctgac aaccgcaaca acaaaaacac aaatccttgg cactggctag 120  
 tctatgtcct ctcaagtgcc tttttgtttg t 151

<210> 55  
 <211> 91  
 <212> DNA  
 <213> Homo sapien

<400> 55  
 acctggcttg tctccgggtg gttcccggcg cccccacgg tccccagaac ggacactttc 60  
 gccctccagt ggatactga gccaaagtgg t 91

<210> 56  
 <211> 133  
 <212> DNA  
 <213> Homo sapien

<400> 56  
 ggccggatgtg cgttgggtat atacaaatat gtcattttat gtaagggact tgagtatact 60  
 tggatttttg gtatctgtgg gttgggggga cgggccagga accaataccc catggatacc 120  
 aagggaacaac tgt 133

<210> 57  
 <211> 147  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)... (147)  
 <223> n = A,T,C or G

<400> 57  
 actctggaga acctgagccg ctgctccgcc tctgggatga ggtgatgcan gcngtggcgc 60  
 gactgggagc tgagcccttc cctttgcgcc tgcctcagag gattgttgcc gacntgcana 120  
 tctcantggg ctggatncat gcagggt 147

<210> 58  
 <211> 198  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)... (198)  
 <223> n = A,T,C or G

<400> 58  
 acagggatat aggtttnaag ttattgtnat tgtaaaatac attgaatttt ctgtatactc 60  
 tgattacata catttatcct ttaaaaaaga tgtaaatctt aatttttatg ccatctatta 120  
 atttaccat gagttacctt gtaaatgaga agtcatgata gcactgaatt ttaactagtt 180  
 ttgacttcta agtttgggt 198

<210> 59  
 <211> 330  
 <212> DNA  
 <213> Homo sapien

<400> 59  
 acaacaaatg ggttgtagg aagtcttattc agcaaaactg gtgatggcta ctgaaaagat 60  
 ccattgaaaa ttatcattaa tgatttttaa tgacaagtta tcaaaaactc actcaatttt 120  
 cacctgtgct agcttgctaa aatgggagtt aactctagag caaatatagt atcttctgaa 180  
 tacagtcaat aaatgacaaa gccagggcct acaggtgggt tccagacttt ccagaccag 240  
 cagaaggaat ctattttatc acatggatct ccgtctgtgc tcaaaatacc taatgatatt 300  
 tttcgtcttt attggacttc tttgaagagt 330

<210> 60  
 <211> 175  
 <212> DNA  
 <213> Homo sapien

<400> 60  
 accgtgggtg cttctacat tcctgacggc tccttcacca acatctggtt ctacttcggc 60  
 gtcgtgggct cttcctctt catcctcctc cagctgggtg tgctcatcga ctttgccgac 120  
 tcctggaacc agcggtaggt gggcaaggcc gaggagtgcg attcccgtgc ctggt 175

<210> 61  
 <211> 154  
 <212> DNA  
 <213> Homo sapien

<400> 61  
 accccacttt tcctcctgtg agcagtctgg acttctcact gctacatgat gagggtagt 60  
 ggttggtgct cttcaacagt atcctcccct ttccggatct gctgagccgg acagcagtgc 120  
 tggactgcac agccccgggg ctccacattg ctgt 154

<210> 62  
 <211> 30  
 <212> DNA  
 <213> Homo sapien

<400> 62  
 cgctcgagcc ctatagttag tcgtattaga 30

<210> 63  
 <211> 89  
 <212> DNA  
 <213> Homo sapien

<400> 63  
 acaagtcatt tcagcaccct ttgctcttca aaactgacca tcttttatat ttaatgcttc 60  
 ctgtatgaat aaaaatggtt atgtcaagt 89

<210> 64  
 <211> 97  
 <212> DNA  
 <213> Homo sapien

<400> 64  
 accggagtaa ctgagtcggg acgctgaatc tgaatccacc aataaataaa ggttctgcag 60

aatcagtgc tccaggattg gtccttggat ctgggggt

97.

<210> 65  
 <211> 377  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1) ... (377)  
 <223> n = A,T,C or G

<400> 65  
 acaacaanaa ntcccttctt taggccactg atggaaacct ggaacccctt tttgatggca 60  
 gcatggcgct ctaggccttg acacageggc tgggggtttg gctntcccaa accgcacacc 120  
 ccaaccctgg tctaccaca nttctggcta tgggctgtct ctgccactga acatcagggg 180  
 tcggtcataa natgaaatcc caanggggac agaggtcagt agaggagct caatgagaaa 240  
 ggtgctgttt gctcagccag aaaacagctg cctggcattc gccgctgaac tatgaacccg 300  
 tgggggtgaa ctaccccan gaggaatcat gcctgggcga tgcaanggtg ccaacaggag 360  
 gggcgggagg agcatgt 377

<210> 66  
 <211> 305  
 <212> DNA  
 <213> Homo sapien

<400> 66  
 acgcctttcc ctccagaattc agggaagaga ctgtcgctg ccttcctccg ttgttgcgtg 60  
 agaacccttg tgcccttcc caccatatcc accctcgctc catctttgaa ctcaaacagc 120  
 aggaactaac tgcacctgg tctctctccc agtccccagt tcacctcca tccctcacct 180  
 tctccactc taagggatat caacactgcc cagcacaggg gccctgaatt tatgtggttt 240  
 ttatatattt ttttaataaga tgcactttat gtcatttttt aataaagtct gaagaattac 300  
 tgttt 305

<210> 67  
 <211> 385  
 <212> DNA  
 <213> Homo sapien

<400> 67  
 actacacaca ctccacttgc ctttgtgaga cactttgtcc cagcacttta ggaatgctga 60  
 ggtcggacca gccacatctc atgtgcaaga ttgccagca gacatcaggt ctgagagttc 120  
 cccttttaaa aaaggggact tgcttaaaaa agaagtctag ccacgattgt gttagagcagc 180  
 tgtgctgtgc tggagattca cttttgagag agttctcctc tgagacctga tctttagagg 240  
 ctgggcagtc ttgcacatga gatgggctg gtctgatctc agcactcctt agtctgcttg 300  
 cctctcccag ggccccagcc tggccacacc tgcttacagg gcactctcag atgccatac 360  
 catagtttct gtgctagtgg accgt 385

<210> 68  
 <211> 73  
 <212> DNA  
 <213> Homo sapien

<400> 68  
 acttaaccag atatatTTTT accccagatg gggatattct ttgtaaaaaa tgaaaataaa 60  
 gtttttttaa tgg 73

<210> 69

<211> 536  
 <212> DNA  
 <213> Homo sapien  
 <220>  
 <221> misc\_feature  
 <222> (1)...(536)  
 <223> n = A,T,C or G

<400> 69  
 actagtccag tgtggtggaa ttccattgtg ttgggggctc tcaccctcct ctctgcagc 60  
 tccagctttg tgctctgcct ctgaggagac catggcccag catctgagta ccctgctgct 120  
 cctgctggcc accctagctg tggccctggc ctggagcccc aaggaggagg ataggataat 180  
 cccgggtggc atctataacg cagacctcaa tgatgagtgg gtacagcgtg cccttcactt 240  
 cgccatcagc gagtataaca aggccaccaa agatgactac tacagacgtc cgctgcgggt 300  
 actaagagcc aggcaacaga ccgttggggg ggtgaattac ttcttcgacg tagagggtgg 360  
 ccgaaccata tgtaccaagt ccagcccaa ctgggacacc tgtgccttcc atgaacagcc 420  
 agaactgcag aagaaacagt tgtgctcttt cgagatctac gaagttccct ggggagaaca 480  
 gaangtccct ggtgaaatc caggtgtcaa gaaatcctan ggatctgttg ccaggc 536

<210> 70  
 <211> 477  
 <212> DNA  
 <213> Homo sapien

<400> 70  
 atgacccta acaggggccc tctcagccct cctaattgacc tccggcctag ccatgtgatt 60  
 tcacttccac tccataacgc tccatatact aggcctacta accaacacac taaccatata 120  
 ccaatgatgg cgcgatgtaa cagagaaaag cacataccaa ggccaccaca caccacctgt 180  
 ccaaaaaggc cttcgatagc ggataatcct atttattacc tcagaagtgt ttttcttcgc 240  
 agggattttt ctgagccttt taccactcca gcctagcccc taccgcccaa ctaggagggc 300  
 actggcccc aacaggcctc accccgctaa atcccctaga agtcccactc ctaaacacat 360  
 ccgtattact cgcacagga gtatcaatca cctgagctca ccatagtcta atagaaaaca 420  
 accgaaacca aattattcaa agcactgctt attacaattt tactgggtct ctatttt 477

<210> 71  
 <211> 533  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(533)  
 <223> n = A,T,C or G

<400> 71  
 agagctatag gtacagtgtg atctcagctt tgcaaacaca ttttctacat agatagtact 60  
 aggtattaat agatatgtaa agaaagaaat cacaccatta ataattgtaa gattggttta 120  
 tgtattttta gtggtatttt tggcaccctt atatatgttt tccaaacttt cagcagtgat 180  
 attattttca taacttaaaa agtgagtttg aaaaagaaaa tctccagcaa gcatctcatt 240  
 taaataaagg tttgtcatct ttaaaaatac agcaatatgt gactttttta aaaagctgtc 300  
 aaatagggtg gaccctacta ataattatta gaaatacatt taaaaacatc gagtacctca 360  
 agtcagtttg ccttgaaaaa tatcaaatat aactcttaga gaaatgtaca taaaagaatg 420  
 cttcgtaatt ttggagtang aggttccctc ctcaattttg tttttttaaa aagtacatgg 480  
 taaaaaaaaa aattcacaac agtatataag gctgtaaaat gaagaattct gcc 533

<210> 72  
 <211> 511

<212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(511)  
 <223> n = A,T,C or G

<400> 72  
 tattacggaa aaacacacca cataattcaa ctancaaaga anactgcttc agggcgtgta 60  
 aaatgaaagg cttccaggca gttatctgat taaagaacac taaaagaggg acaaggctaa 120  
 aagccgcagg atgtctacac tatancaggc gctatttggg ttggctggag gagctgtgga 180  
 aaacatggan agattgggtgc tgganatcgc cgtggctatt cctcattgtt attacanagt 240  
 gaggttctct gtgtgcccac tggtttgaaa accgttctnc aataatgata gaatagtaca 300  
 cacatgagaa ctgaaatggc ccaaaccagc aaagaaagcc caactagatc ctcagaanac 360  
 gcttctaggg acaataaccg atgaagaaaa gatggcctcc ttgtgcccc gtctgttatg 420  
 attctctccc attgcagcna naaaccggtt cttctaagca aacncagggt atgatggcna 480  
 aaatacaccc cctcttgaag naccnggagg a 511

<210> 73  
 <211> 499  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(499)  
 <223> n = A,T,C or G

<400> 73  
 cagtgccagc actgggtgcc gtaccagtac caataacagt gccagtgcc gtgccagcac 60  
 cagtgggtgc ttcagtgtcg gtgccagcct gaccgccact ctcacatttg ggctcttcgc 120  
 tggccttggt ggagctgggt ccagcaccag tggcagctct ggtgcctgtg gtttctccta 180  
 caagtgagat ttagatatt gttaatcctg ccagtcttct tcttcaagcc aggggtgcac 240  
 ctcagaaacc tactcaacac agcactctag gcagccacta tcaatcaatt gaagttagaca 300  
 ctctgcatta aatctatttg ccatttctga aaaaaaaaaa aaaaaaaggc cgcccgctcg 360  
 antctagagg gcccggttaa acccgctgat cagcctcgac tgtgccttct anttgccagc 420  
 catctgttgt ttgccctccc cccgntgcct tccttgacct tggaaagtgc cactcccact 480  
 gtcccttcct aantaaat 499

<210> 74  
 <211> 537  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(537)  
 <223> n = A,T,C or G

<400> 74  
 tttcatagga gaacacactg aggagatact tgaagaattt ggattcagcc gcgaagagat 60  
 ttatcagctt aactcagata aaatcattga aagtaataag gtaaaagcta gtctctaact 120  
 tccaggccca cggtcaagt gaatttgaat actgcattta cagtgtagag taacacataa 180  
 cattgtatgc atggaaacat ggaggaacag tattacagtg tcctaccact ctaatcaaga 240  
 aaagaattac agactctgat tctacagtga tgattgaatt ctaaaaatgg taatcattag 300  
 ggcttttgat ttataanact ttgggtactt atactaaatt atggtagtta tactgccttc 360  
 cagtttgctt gatataattt ttgatattaa gattcttgac ttatattttg aatgggttct 420



actgaaaaan gaatgatata ttcttgaaga catcgatata catttattta cactcttgat 480  
tctacaatgt agaaaatgaa ggaaatgccc caaattgtat ggtgataaaa gtcccgt 537

<210> 75  
<211> 467  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(467)  
<223> n = A,T,C or G

<400> 75  
caaanacaat tgttcaaaaag atgcaaataga tacactactg ctgcagctca caaacacctc 60  
tgcataattac acgtacctcc tctgtctcct caagtagtgt ggtctatttt gccatcatca 120  
cctgctgtct gcttagaaga acggctttct gctgcaangg agagaaatca taacagacgg 180  
tggcacaagg aggccatctt ttctcatcgc gttattgtcc ctagaagcgt cttctgagga 240  
tctagtggg ctttctttct gggtttgggc catttcantt ctcatgtgtg tactattcta 300  
tcattattgt ataacggttt tcaaaccngt gggcacncag agaacctcac tctgtaataa 360  
caatgaggaa tagccacggg gatctccagc accaaatctc tccatgttnt tccagagctc 420  
ctccagccaa cccaaatagc cgctgctatn gtgtagaaca tccctgn 467

<210> 76  
<211> 400  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(400)  
<223> n = A,T,C or G

<400> 76  
aagctgacag cattcgggcc gagatgtctc gctccgtggc cttagctgtg ctgcgcgtac 60  
tctctctttc tggcctggag gctatccagc gtactccaaa gattcaggtt tactcacgtc 120  
atccagcaga gaattgaaaag tcaaatttcc tgaattgcta tgtgtctggg tttcatccat 180  
ccgacattga agttgactta ctgaagaatg gagagagaat tgaaaaagtg gagcattcag 240  
acttgtcttt cagcaaggac tgggtctttct atctcttgta ctacactgaa ttcaccccca 300  
ctgaaaaaga tgagtatgcc tgccgtgtga accatgtgac tttgtcacag cccaagatng 360  
ttnagtggga toganacatg taagcagcan catgggaggt 400

<210> 77  
<211> 248  
<212> DNA  
<213> Homo sapien

<400> 77  
ctggagtgcc ttggtgtttc aagcccctgc aggaagcaga atgcaccttc tgaggcacct 60  
ccagctgccc cggcggggga tgcgaggctc ggagcacctt tgcccggctg tgattgtctg 120  
caggcactgt tcatctcagc ttttctgtcc ctttgcctcc ggcaagcgt tctgtgaaa 180  
gttcatatct ggagcctgat gtcttaacga ataaaggtcc catgctccac ccgaaaaaaa 240  
aaaaaaaa 248

<210> 78  
<211> 201  
<212> DNA  
<213> Homo sapien

<400> 78  
 actagtccag tgtggtggaa ttccattgtg ttggggcccaa cacaatggct acctttaaca 60  
 tcaccagac cccgccctgc cegtgcccca cgctgctgct aacgacagta tgatgcttac 120  
 tctgtactc ggaaactatt tttatgtaat taatgtatgc tttcttgttt ataaatgcct 180  
 gatttaaaaa aaaaaaaaaa a 201

<210> 79  
 <211> 552  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(552)  
 <223> n = A,T,C or G

<400> 79  
 tccttttggt aggtttttga gacaacccta gacctaaact gtgtcacaga cttctgaatg 60  
 tttaggcagt gctagtaatt tcctcgtaat gattctgtta ttactttcct attctttatt 120  
 cctctttctt ctgaagatta atgaagttga aaattgaggt ggataaatac aaaaaggtag 180  
 tgtgatagta taagtatcta agtgcagatg aaagtgtgtt atatatatcc attcaaaatt 240  
 atgcaagtta gtaattactc agggttaact aaattacttt aatatgctgt tgaacctact 300  
 ctgttccttg gctagaaaaa attataaaca ggactttgtt agtttgggaa gccaaattga 360  
 taatattcta tgttctaaaa gttgggctat acataaanta tnaagaaata tggaatttta 420  
 ttcccaggaa tatgggggttc atttatgaat antaccggg anagaagttt tgantnaaac 480  
 cngttttggt taatacgta atagtctctn aatnaacaag gcntgactta tttccaaaaa 540  
 aaaaaaaaaa aa 552

<210> 80  
 <211> 476  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(476)  
 <223> n = A,T,C or G

<400> 80  
 acagggattt gagatgctaa ggccccagag atcgtttgat ccaaccctct tattttcaga 60  
 ggggaaaaatg gggcctagaa gttacagagc atctagctgg tgcgctggca cccctggcct 120  
 cacacagact cccgagtagc tgggactaca ggcacacagt cactgaagca ggccctgttt 180  
 gcaattcacg ttgccacctc caacttaaac attcttcata tgtgatgtcc ttagtcacta 240  
 aggttaaact ttcccacca gaaaaggcaa cttagataaa atcttagagt actttcatac 300  
 tcttctaagt cctcttcag cctcactttg agtcctcctt ggggggttgat aggaantntc 360  
 tcttggtttt ctcaataaaa tctctatcca tctcatgttt aatttgggtac gcntaaaaat 420  
 gctgaaaaaa ttaaatgtt ctggtttcnc tttaaaaaa aaaaaaaaaa aaaaaa 476

<210> 81  
 <211> 232  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(232)  
 <223> n = A,T,C or G

```

<400> 81
tttttttttg tatgcntcn ctgtgngtt attgttgctg ccacctgga ggagcccagt    60
ttcttctgta tctttctttt ctgggggatc ttcttggtc tgccctcca ttccagcct    120
ctcatcccca tcttgactt ttgctagggt tggaggcgct ttcttggtag cccctcagag    180
actcagtcag cgggaataag tcctaggggt ggggggtgtg gcaagccggc ct          232

```

```

<210> 82
<211> 383
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(383)
<223> n = A,T,C or G

```

```

<400> 82
aggcgggagc agaagctaaa gccaaagccc aagaagagtg gcagtgccag cactggtgcc    60
agtaccagta ccaataacat gccagtgccg gtgccagcac cagtgggtggc ttcagtgtg    120
gtgccagcct gaccgccact ctacatttg ggctcttcgc tggccttggt ggagctgggt    180
ccagcaccag tggcagctct ggtgcctgtg gtttctccta caagtgagat tttagatatt    240
gttaatcctg ccagctcttc tcttcaagcc aggggtgcac ctcagaaacc tactcaacac    300
agcactctng gcagccacta tcaatcaatt gaagttgaca ctctgcatta aatctatttg    360
ccatttcaaa aaaaaaaaaa aaa          383

```

```

<210> 83
<211> 494
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(494)
<223> n = A,T,C or G

```

```

<400> 83
accgaattgg gaccgtggc ttataagcga tcatgtctc cagtattacc tcaacgagca    60
gggagatcga gtctatacgc tgaagaaatt tgaccgatg ggacaacaga cctgtctcagc    120
ccatctgtct cggttctccc cagatgacaa atactctcga caccgaatca ccatcaagaa    180
acgcttcaag gtgctcatga ccagcaacc gcgccctgtc ctctgagggt ccttaaactg    240
atgtcttttc tgccacctgt taccctcgg agactccgta accaaactct tcggactgtg    300
agccctgatg cttttttgcc agccatactc tttggentcc agtctctcgt gccgattgat    360
tatgcttggt tgaggcaatc atggtggcat caccatnaa gggaacacat ttganttttt    420
tttncatat tttaaattac naccagaata nttcagaata aatgaattga aaaactctta    480
aaaaaaaaaa aaaa          494

```

```

<210> 84
<211> 380
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(380)
<223> n = A,T,C or G

```

```

<400> 84

```

```

gctggtagcc tatggcgtgg ccacggangg gctcctgagg cacgggacag tgacttccca    60
agtatcctgc gcgcgctctt ctaccgtccc tacctgcaga tcttcgggca gattccccag    120
gaggacatgg acgtggccct catggagcac agcaactgct cgtcggagcc cggcttctgg    180
gcacaccctc ctggggccca ggccggcacc tgcgtctccc agtatgccaa ctggctggtg    240
gtgctgctcc tcgtcatctt cctgctcgtg gccaacatcc tgctggtcac ttgctcattg    300
ccatgttcag ttacacattc ggcaaagtac agggcaacag cnatctctac tgggaaggcc    360
agcgtnccg cctcatccgg                                     380

```

```

<210> 85
<211> 481
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(481)
<223> n = A,T,C or G

```

```

<400> 85
gagttagctc ctccacaacc ttgatgaggt cgtctgcagt ggctctcgc ttcataccgc    60
tnccatcgtc atactgtagg ttggccacca cctcctgcat cttggggcgg ctaatatcca    120
ggaaactctc aatcaagtca ccgtnatna aacctgtggc tggttctgtc ttccgctcgg    180
tgtgaaagga tctccagaag gagtgtctga tcttcccac acttttgatg actttattga    240
gtcgattctg catgtccagc aggaggttgt accagctctc tgacagttag gtcaccagcc    300
ctatcatgcc nttgaacgtg ccgaagaaca ccgagccttg tgtggggggg gnagtctcac    360
ccagattctg cattaccaga nagccgtggc aaaaganatt gacaactcgc ccaggnngaa    420
aaagaacacc tcctggaagt gctngccgct cctcgtcent tgggtggngc gcntnccttt    480
t                                                                481

```

```

<210> 86
<211> 472
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(472)
<223> n = A,T,C or G

```

```

<400> 86
aacatcttcc tgtataatgc tgtgtaatat cgatccgatn ttgtctgctg agaattcatt    60
acttgaaaaa gcaacttnaa gcctggacac tggattaaaa attcacaata tgcaacactt    120
taaacagtgt gtcaatctgc tcccttactt tgtcatcacc agtctgggaa taagggtatg    180
ccctattcac acctgttaaa agggcgctaa gcatttttga ttcaacatct ttttttttga    240
cacaagtcgg aaaaaagcaa aagtaaacag ttnttaattt gtagccaat tcactttctt    300
catgggacag agccatttga tttaaaaagc aaattgcata atattgagct ttgggagctg    360
atatntgagc ggaagantag cttttctact tcaccagaca caactccttt catattggga    420
tgtnnacnaa agttatgtct cttacagatg ggatgctttt gtggcaattc tg                472

```

```

<210> 87
<211> 413
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(413)
<223> n = A,T,C or G

```

<400> 87  
 agaaaccagt atctctnaaa acaacctctc ataccttggt gacctaatTT tgtgtgcgtg 60  
 tgtgtgtgcg cgcataattat atagacaggc acatcttttt tacttttgta aaagcttatg 120  
 cctcttttgg atctatatct gtgaaagttt taatgatctg ccataatgtc ttggggacct 180  
 ttgtcttctg tgtaaattggt actagagaaa acacctatnt tatgagtcaa tctagttngt 240  
 ttatttcgac atgaaggaaa ttccagatn acaactna caaactctcc cttgactagg 300  
 ggggacaaaag aaaagcanaa ctgaacatna gaaacaatn cctggtgaga aattncataa 360  
 acagaaattg ggtngtatat tgaaanann catcattnaa acgttttttt ttt 413

<210> 88  
 <211> 448  
 <212> DNA  
 <213> Homo sapien  
 <220>  
 <221> misc\_feature  
 <222> (1)...(448)  
 <223> n = A,T,C or G

<400> 88  
 cgcagcgggt cctctctatc tagctccagc ctctcgctg cccactccc cgcgtcccgc 60  
 gtcctagccn accatggccg ggcccctgcg cgcccgcgtg ctctgctgg ccacctggc 120  
 cgtggccctg gccgtgagcc ccgcggcccg ctccagctcc ggcaagccgc cgcgcctggt 180  
 gggaggccca tggaccccgc gtggaagaag aagggtgctg gcgtgcaactg gactttgccg 240  
 tcgcnanta caacaaaccc gcaacnactt ttaccnagcn cgcgctgcag gttgtgccgc 300  
 cccaancaaa ttgttactng gggtaantaa ttcttggaag ttgaacctgg gccaaacnng 360  
 ttaccagaa ccnagccaat tngaacaatt ncccctccat aacagcccct tttaaaaagg 420  
 gaancantcc tgnctctttc caaatTTT 448

<210> 89  
 <211> 463  
 <212> DNA  
 <213> Homo sapien  
 <220>  
 <221> misc\_feature  
 <222> (1)...(463)  
 <223> n = A,T,C or G

<400> 89  
 gaattttgtg cactggccac tgtgatggaa ccattgggcc aggatgcttt gagtttatca 60  
 gtagtgattc tgccaaagtt ggtgttgtaa catgagtatg taaaatgtca aaaaatttagc 120  
 agaggtctag gtctgcatat cagcagacag ttgtccgtg tattttgtag ccttgaagtt 180  
 ctcaagtaca agttnnttct gatgcgaagt tctnattcca gtgttttagt cctttgcac 240  
 tttnatgtn agacttgccct ctntnaaatt gcttttgnt tctgcaggta ctatctgtgg 300  
 ttaacaaaa tagaannact tctctgcttn gaanatttga atatcttaca tctnaaaatn 360  
 aattctctcc ccatannaaa acccangccc ttggganaat ttgaaaaang gntccttcnn 420  
 aattcnana anttcagntn tcatacaaca naacngganc ccc 463

<210> 90  
 <211> 400  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(400)

<223> n = A,T,C or G

<400> 90

agggattgaa	ggtctnttnt	actgtcggac	tggtcancca	ccaactctac	aagttgctgt	60
cttccactca	ctgtctgtaa	gcntnttaac	ccagactgta	tcttcataaa	tagaacaaat	120
tcttcaccag	tcacatcttc	taggaccttt	ttggattcag	ttagtataag	ctcttccact	180
tcctttgtta	agacttcate	tggtaaagtc	ttaagttttg	tagaaaggaa	tttaattgct	240
cgttctctaa	caatgtcctc	tccttgaagt	atttggtctg	acaaccacc	tnaagtcct	300
ttgtgcatcc	attttaaata	tacttaatag	ggcattggtg	cactagggtta	aattctgcaa	360
gagtcactctg	tctgcaaaag	ttgcgttagt	atatctgcc			400

<210> 91

<211> 480

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(480)

<223> n = A,T,C or G

<400> 91

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atgcctcttt	gactaccgtg	tgccagtgtc	gggtattctc	acacacctcc	nnccgctctt	180
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gacacttgaa	aggtgtaaca	aagcgactct	tgcatgtgtt	tttgtccctc	cggcaccagt	300
tgtcaatact	aacccgctgg	tttgccctcca	tcacatttgt	gatctgtagc	tctggatata	360
tctcctgaca	gtactgaaga	acttcttctt	ttgtttcaaa	agcaactctt	ggtgcctgtt	420
ngatcaggtt	cccatttccc	agtcogaatg	ttcacatggc	atatnttact	tcccacaaaa	480

<210> 92

<211> 477

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(477)

<223> n = A,T,C or G

<400> 92

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cccacgcagg	cagcagcggg	gccggtcaat	gaactccact	cgtggcttgg	ggttgacggt	180
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tgacagcaaa	ctcctcgatg	gtcatgagcg	ggaagcgaat	gangcccagg	gccttgccca	300
gaaccttccg	cctgttctct	ggcgtcacct	gcagctgctg	ccgctnacac	tcggcctcgg	360
accagcggac	aaacggcggt	gaacagcgcg	acctcacgga	tgcccantgt	gtcgcgctcc	420
aggaacggcn	ccagcgtgtc	caggtcaatg	tcggtgaanc	ctccgcgggt	aatggcg	477

<210> 93

<211> 377

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

&lt;222&gt; (1)...(377)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 93

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agtccgagca	gccccagacc	gctgccgccc	gaagctaagc	ctgcctctgg	ccttccccctc	120
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tgattttact	tggaatttc	ctctgttata	tagcttttcc	caatgctaata	ttccaaacaa	240
caacaacaaa	ataacatgtt	tgctgttna	gttgataaaa	agtangtgat	tctgtatnta	300
aagaaaatat	tactgttaca	tatactgctt	gcaanttctg	tattttattgg	tnctctggaa	360
ataaatatat	tattaaa					377

&lt;210&gt; 94

&lt;211&gt; 495

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(495)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 94

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cgagctgang	cagatttccc	acagtgaccc	cagagccctg	ggctatagtc	tctgacccct	120
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gaaggcccca	ttccggggct	gttccccgag	gaggaaggga	aggggctctg	tgtgccccc	240
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acacccaccc	agancancca	cccgccatgg	ggaatgtnct	caaggaatcg	cngggcaacg	420
tggaactctng	tcccnnaagg	gggcagaatc	tccaatagan	gganngaacc	cttgctnana	480
aaaaaaaaana	aaaaa					495

&lt;210&gt; 95

&lt;211&gt; 472

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(472)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 95

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cctctggaag	ccttgccgag	agcggacttt	gtaattgttg	gagaataact	gctgaatttt	120
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tatttattat	cttgtgaaaa	gtatacaatg	aaaattttgt	tcatactgta	tttatcaagt	240
atgatgaaaa	gcaatagata	tatattcttt	tattatgttn	aattatgatt	gccattatta	300
atcggaacaa	tgtggagtgt	atgttctttt	cacagtaata	tatgcctttt	gtaacttcac	360
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&lt;210&gt; 96

&lt;211&gt; 476

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

<220>  
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 <222> (1)...(476)  
 <223> n = A,T,C or G

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 ttttaactca tgattttttac acacacaatc cagaacttat tatatagcct ctaagtcttt 180  
 attcttcaca gtagatgatg aaagagtcct ccagtgtctt gngcanaatg ttctagnat 240  
 agctggatac atacngtggg agttctataa actcatacct cagtgggact naaccaaaat 300  
 tgtgttagtc tcaattccta ccacactgag ggagcctccc aaatcactat attcttatct 360  
 gcaggtactc ctccagaaaa acngacaggg caggcttgca tgaaaaagtn acatctgcgt 420  
 tacaaaagtct atcttctcta nangtctgtt aaggaacaat ttaatcttct agcttt 476

<210> 97  
 <211> 479  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(479)  
 <223> n = A,T,C or G

<400> 97  
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 caatcgcaaa tcaaaaactca caagtgtctca tctgttgtag atttagtgta ataagactta 180  
 gattgtgctc ctctcgatat gattgtttct canatcttgg gcaatnttcc ttagtcaaatt 240  
 caggctacta gaattctgtt attggatatn tgagagcatg aaatttttaa naatacactt 300  
 gtgattatna aattaatcac aaatttcaact tatacctgct atcagcagct agaaaaacat 360  
 ntnnttttta natcaaagta ttttgtgttt ggaantgttn aaatgaaatc tgaatgtggg 420  
 ttcnatctta ttttttcccn gacnactant tnccttttta gggncatttc tganccatc 479

<210> 98  
 <211> 461  
 <212> DNA  
 <213> Homo sapien

<400> 98  
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 tcaactccag ctggattatt ttggagcctg caaatctatt cctacttgta cggactttga 180  
 agtgattcag tttcctctac ggatgagaga ctggctcaag aatatcctca tgcagcttta 240  
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 ttacctggag aaaagaggct ttggctgggg accatcccat tgaaccttct cttaggact 360  
 ttaagaaaaa ctaccacatg ttgtgtatcc tgggtccggc cgtttatgaa ctgaccacc 420  
 tttggaataa tcttgacgct cctgaacttg ctctctgcyg a 461

<210> 99  
 <211> 171  
 <212> DNA  
 <213> Homo sapien

<400> 99  
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cggtgagaaa agccttctct agcgatctga gaggcgtgcc ttgggggtac c 171

<210> 100  
 <211> 269  
 <212> DNA  
 <213> Homo sapien

<400> 100  
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 aaggctgagc tgacgccgca gaggtcgtgt cacgtccac gaccttgacg ccgtcgggga 180  
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 cgagagatac gcaggtgcag gtggccgccc 269

<210> 101  
 <211> 405  
 <212> DNA  
 <213> Homo sapien

<400> 101  
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 ctgttctgga gggagattag ggtttcttgc caaatccaac aaaatccact gaaaaagtgt 360  
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<210> 102  
 <211> 470  
 <212> DNA  
 <213> Homo sapien

<400> 102  
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 tcaaatctta aattattcaa attagccaaa tccttaccac ataataccca aaaatcaaaa 180  
 atatacttct ttacgcaaac ttgttacata aattaaaaaa atatatacgg ctggtgtttt 240  
 caaagtacaa ttatcttaac actgcaaaac ttttaaggaa ctaaaataaa aaaaaacact 300  
 ccgcaaaggt taaagggaac aacaaattct tttacaacac cattataaaa atcatatctc 360  
 aaatcttagg ggaatatata cttcacacgg gatcttaact tttactcact ttgtttattt 420  
 ttttaacca ttgtttgggc ccaacacaat ggaatcccc ctggactagt 470

<210> 103  
 <211> 581  
 <212> DNA  
 <213> Homo sapien

<400> 103  
 tttttttttt ttttttttga cccctctctt ataaaaaaca agttaccatt ttattttact 60  
 tacacatatt tattttataa ttggtattag atattcaaaa ggcagctttt aaaatcaaac 120  
 taaatggaaa ctgccttaga tacataatc ttaggaatta gcttaaaatc tgccataagt 180  
 gaaaatcttc tctagctctt ttgactgtaa atttttgact cttgtaaaac atccaaattc 240  
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 gcttctctag cctcatttcc tagctcttat ctactattag taagtggcct ttttcctaaa 360  
 agggaaaaca ggaagagaaa tggcacacaa aacaaacatt ttatattcat atttctacct 420  
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581

<210> 104  
<211> 578  
<212> DNA  
<213> Homo sapien

<400> 104

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<210> 105  
<211> 538  
<212> DNA  
<213> Homo sapien

<400> 105

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ggcgagaaat	gaggaagaaa	agaaaaggat	tacgcatact	gttctttcta	tggaaggatt	480
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<210> 106  
<211> 473  
<212> DNA  
<213> Homo sapien

<400> 106

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<210> 107  
<211> 1621  
<212> DNA  
<213> Homo sapien

<400> 107

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a 1621

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&lt;210&gt; 108

&lt;211&gt; 382

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 108

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Met Ala Leu Gln Gly Ile Ser Val Met Glu Leu Ser Gly Leu Ala Pro
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20     25     30
Arg Val Asp Arg Pro Gly Ser Arg Tyr Asp Val Ser Arg Leu Gly Arg
35     40     45
Gly Lys Arg Ser Leu Val Leu Asp Leu Lys Gln Pro Arg Gly Ala Ala
50     55     60
Val Leu Arg Arg Leu Cys Lys Arg Ser Asp Val Leu Leu Glu Pro Phe
65     70     75     80
Arg Arg Gly Val Met Glu Lys Leu Gln Leu Gly Pro Glu Ile Leu Gln
85     90     95
Arg Glu Asn Pro Arg Leu Ile Tyr Ala Arg Leu Ser Gly Phe Gly Gln
100    105    110
Ser Gly Ser Phe Cys Arg Leu Ala Gly His Asp Ile Asn Tyr Leu Ala
115    120    125
Leu Ser Gly Val Leu Ser Lys Ile Gly Arg Ser Gly Glu Asn Pro Tyr
130    135    140
Ala Pro Leu Asn Leu Leu Ala Asp Phe Ala Gly Gly Gly Leu Met Cys
145    150    155    160
Ala Leu Gly Ile Ile Met Ala Leu Phe Asp Arg Thr Arg Thr Asp Lys
165    170    175
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180    185    190
Ser Phe Leu Trp Lys Thr Gln Lys Ser Ser Leu Trp Glu Ala Pro Arg

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195	200	205
Gly Gln Asn Met Leu Asp	Gly Gly Ala Pro Phe	Tyr Thr Thr Tyr Arg
210	215	220
Thr Ala Asp Gly Glu Phe	Met Ala Val Gly Ala	Ile Glu Pro Gln Phe
225	230	235
Tyr Glu Leu Leu Ile Lys	Gly Leu Gly Leu Lys	Ser Asp Glu Leu Pro
245	250	255
Asn Gln Met Ser Met Asp	Asp Trp Pro Glu Met	Lys Lys Lys Phe Ala
260	265	270
Asp Val Phe Ala Lys Lys	Thr Lys Ala Glu Trp	Cys Gln Ile Phe Asp
275	280	285
Gly Thr Asp Ala Cys Val	Thr Pro Val Leu Thr	Phe Glu Glu Val Val
290	295	300
His His Asp His Asn Lys	Glu Arg Gly Ser Phe	Ile Thr Ser Glu Glu
305	310	315
Gln Asp Val Ser Pro Arg	Pro Ala Pro Leu Leu	Leu Asn Thr Pro Ala
325	330	335
Ile Pro Ser Phe Lys Arg	Asp Pro Phe Ile Gly	Glu His Thr Glu Glu
340	345	350
Ile Leu Glu Glu Phe Gly	Phe Ser Arg Glu Glu	Ile Tyr Gln Leu Asn
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<210> 109  
 <211> 1524  
 <212> DNA  
 <213> Homo sapien

<400> 109

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<211> 3410  
 <212> DNA  
 <213> Homo sapien

<400> 110

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 <211> 1289  
 <212> DNA  
 <213> Homo sapien

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<210> 112  
 <211> 315  
 <212> PRT  
 <213> Homo sapien

<400> 112																	
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Leu	Gly	Pro	Lys	Ile	Val	Ile	Val	Ser	Lys	Met	Met	Lys	Asp	Val	Phe		
			20					25					30				
Phe	Phe	Leu	Phe	Phe	Leu	Gly	Val	Trp	Leu	Val	Ala	Tyr	Gly	Val	Ala		
			35				40					45					
Thr	Glu	Gly	Leu	Leu	Arg	Pro	Arg	Asp	Ser	Asp	Phe	Pro	Ser	Ile	Leu		
			50			55					60						
Arg	Arg	Val	Phe	Tyr	Arg	Pro	Tyr	Leu	Gln	Ile	Phe	Gly	Gln	Ile	Pro		
65					70				75					80			
Gln	Glu	Asp	Met	Asp	Val	Ala	Leu	Met	Glu	His	Ser	Asn	Cys	Ser	Ser		
			85					90						95			
Glu	Pro	Gly	Phe	Trp	Ala	His	Pro	Pro	Gly	Ala	Gln	Ala	Gly	Thr	Cys		
			100				105					110					
Val	Ser	Gln	Tyr	Ala	Asn	Trp	Leu	Val	Val	Leu	Leu	Leu	Val	Ile	Phe		
			115			120						125					
Leu	Leu	Val	Ala	Asn	Ile	Leu	Leu	Val	Asn	Leu	Leu	Ile	Ala	Met	Phe		
130					135							140					

Ser Tyr Thr Phe Gly Lys Val Gln Gly Asn Ser Asp Leu Tyr Trp Lys  
 145 150 155 160  
 Ala Gln Arg Tyr Arg Leu Ile Arg Glu Phe His Ser Arg Pro Ala Leu  
 165 170 175  
 Ala Pro Pro Phe Ile Val Ile Ser His Leu Arg Leu Leu Arg Gln  
 180 185 190  
 Leu Cys Arg Arg Pro Arg Ser Pro Gln Pro Ser Ser Pro Ala Leu Glu  
 195 200 205  
 His Phe Arg Val Tyr Leu Ser Lys Glu Ala Glu Arg Lys Leu Leu Thr  
 210 215 220  
 Trp Glu Ser Val His Lys Glu Asn Phe Leu Leu Ala Arg Ala Arg Asp  
 225 230 235 240  
 Lys Arg Glu Ser Asp Ser Glu Arg Leu Lys Arg Thr Ser Gln Lys Val  
 245 250 255  
 Asp Leu Ala Leu Lys Gln Leu Gly His Ile Arg Glu Tyr Glu Gln Arg  
 260 265 270  
 Leu Lys Val Leu Glu Arg Glu Val Gln Gln Cys Ser Arg Val Leu Gly  
 275 280 285  
 Trp Val Ala Glu Ala Leu Ser Arg Ser Ala Leu Leu Pro Pro Gly Gly  
 290 295 300  
 Pro Pro Pro Pro Asp Leu Pro Gly Ser Lys Asp  
 305 310 315

&lt;210&gt; 113

&lt;211&gt; 553

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 113

Met Val Gln Arg Leu Trp Val Ser Arg Leu Leu Arg His Arg Lys Ala  
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 Gln Leu Leu Leu Val Asn Leu Leu Thr Phe Gly Leu Glu Val Cys Leu  
 20 25 30  
 Ala Ala Gly Ile Thr Tyr Val Pro Leu Leu Leu Glu Val Gly Val  
 35 40 45  
 Glu Glu Lys Phe Met Thr Met Val Leu Gly Ile Gly Pro Val Leu Gly  
 50 55 60  
 Leu Val Cys Val Pro Leu Leu Gly Ser Ala Ser Asp His Trp Arg Gly  
 65 70 75 80  
 Arg Tyr Gly Arg Arg Arg Pro Phe Ile Trp Ala Leu Ser Leu Gly Ile  
 85 90 95  
 Leu Leu Ser Leu Phe Leu Ile Pro Arg Ala Gly Trp Leu Ala Gly Leu  
 100 105 110  
 Leu Cys Pro Asp Pro Arg Pro Leu Glu Leu Ala Leu Leu Ile Leu Gly  
 115 120 125  
 Val Gly Leu Leu Asp Phe Cys Gly Gln Val Cys Phe Thr Pro Leu Glu  
 130 135 140  
 Ala Leu Leu Ser Asp Leu Phe Arg Asp Pro Asp His Cys Arg Gln Ala  
 145 150 155 160  
 Tyr Ser Val Tyr Ala Phe Met Ile Ser Leu Gly Gly Cys Leu Gly Tyr  
 165 170 175  
 Leu Leu Pro Ala Ile Asp Trp Asp Thr Ser Ala Leu Ala Pro Tyr Leu  
 180 185 190  
 Gly Thr Gln Glu Glu Cys Leu Phe Gly Leu Leu Thr Leu Ile Phe Leu  
 195 200 205  
 Thr Cys Val Ala Ala Thr Leu Leu Val Ala Glu Glu Ala Ala Leu Gly  
 210 215 220  
 Pro Thr Glu Pro Ala Glu Gly Leu Ser Ala Pro Ser Leu Ser Pro His

225                                      230                                      235                                      240  
 Cys Cys Pro Cys Arg Ala Arg Leu Ala Phe Arg Asn Leu Gly Ala Leu  
    245                                      250                                      255  
 Leu Pro Arg Leu His Gln Leu Cys Cys Arg Met Pro Arg Thr Leu Arg  
    260                                      265                                      270  
 Arg Leu Phe Val Ala Glu Leu Cys Ser Trp Met Ala Leu Met Thr Phe  
    275                                      280                                      285  
 Thr Leu Phe Tyr Thr Asp Phe Val Gly Glu Gly Leu Tyr Gln Gly Val  
    290                                      295                                      300  
 Pro Arg Ala Glu Pro Gly Thr Glu Ala Arg Arg His Tyr Asp Glu Gly  
 305                                      310                                      315                                      320  
 Val Arg Met Gly Ser Leu Gly Leu Phe Leu Gln Cys Ala Ile Ser Leu  
    325                                      330                                      335  
 Val Phe Ser Leu Val Met Asp Arg Leu Val Gln Arg Phe Gly Thr Arg  
    340                                      345                                      350  
 Ala Val Tyr Leu Ala Ser Val Ala Ala Phe Pro Val Ala Ala Gly Ala  
    355                                      360                                      365  
 Thr Cys Leu Ser His Ser Val Ala Val Val Thr Ala Ser Ala Ala Leu  
 370                                      375                                      380  
 Thr Gly Phe Thr Phe Ser Ala Leu Gln Ile Leu Pro Tyr Thr Leu Ala  
 385                                      390                                      395                                      400  
 Ser Leu Tyr His Arg Glu Lys Gln Val Phe Leu Pro Lys Tyr Arg Gly  
    405                                      410                                      415  
 Asp Thr Gly Gly Ala Ser Ser Glu Asp Ser Leu Met Thr Ser Phe Leu  
    420                                      425                                      430  
 Pro Gly Pro Lys Pro Gly Ala Pro Phe Pro Asn Gly His Val Gly Ala  
    435                                      440                                      445  
 Gly Gly Ser Gly Leu Leu Pro Pro Pro Ala Leu Cys Gly Ala Ser  
 450                                      455                                      460  
 Ala Cys Asp Val Ser Val Arg Val Val Val Gly Glu Pro Thr Glu Ala  
 465                                      470                                      475                                      480  
 Arg Val Val Pro Gly Arg Gly Ile Cys Leu Asp Leu Ala Ile Leu Asp  
    485                                      490                                      495  
 Ser Ala Phe Leu Leu Ser Gln Val Ala Pro Ser Leu Phe Met Gly Ser  
    500                                      505                                      510  
 Ile Val Gln Leu Ser Gln Ser Val Thr Ala Tyr Met Val Ser Ala Ala  
    515                                      520                                      525  
 Gly Leu Gly Leu Val Ala Ile Tyr Phe Ala Thr Gln Val Val Phe Asp  
 530                                      535                                      540  
 Lys Ser Asp Leu Ala Lys Tyr Ser Ala  
 545                                      550

&lt;210&gt; 114

&lt;211&gt; 241

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 114

Met Gln Cys Phe Ser Phe Ile Lys Thr Met Met Ile Leu Phe Asn Leu  
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 Leu Ile Phe Leu Cys Gly Ala Ala Leu Leu Ala Val Gly Ile Trp Val  
    20                                      25                                      30  
 Ser Ile Asp Gly Ala Ser Phe Leu Lys Ile Phe Gly Pro Leu Ser Ser  
    35                                      40                                      45  
 Ser Ala Met Gln Phe Val Asn Val Gly Tyr Phe Leu Ile Ala Ala Gly  
 50                                      55                                      60  
 Val Val Val Phe Ala Leu Gly Phe Leu Gly Cys Tyr Gly Ala Lys Thr  
 65                                      70                                      75                                      80



Glu Ser Lys Cys Ala Leu Val Thr Phe Phe Phe Ile Leu Leu Leu Ile  
                             85                            90                            95  
 Phe Ile Ala Glu Val Ala Ala Ala Val Val Ala Leu Val Tyr Thr Thr  
                             100                            105                            110  
 Met Ala Glu His Phe Leu Thr Leu Leu Val Val Pro Ala Ile Lys Lys  
                             115                            120                            125  
 Asp Tyr Gly Ser Gln Glu Asp Phe Thr Gln Val Trp Asn Thr Thr Met  
                             130                            135                            140  
 Lys Gly Leu Lys Cys Cys Gly Phe Thr Asn Tyr Thr Asp Phe Glu Asp  
                             145                            150                            155                            160  
 Ser Pro Tyr Phe Lys Glu Asn Ser Ala Phe Pro Pro Phe Cys Cys Asn  
                             165                            170                            175  
 Asp Asn Val Thr Asn Thr Ala Asn Glu Thr Cys Thr Lys Gln Lys Ala  
                             180                            185                            190  
 His Asp Gln Lys Val Glu Gly Cys Phe Asn Gln Leu Leu Tyr Asp Ile  
                             195                            200                            205  
 Arg Thr Asn Ala Val Thr Val Gly Gly Val Ala Ala Gly Ile Gly Gly  
                             210                            215                            220  
 Leu Glu Leu Ala Ala Met Ile Val Ser Met Tyr Leu Tyr Cys Asn Leu  
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 Gln

<210> 115  
 <211> 366  
 <212> DNA  
 <213> Homo sapien

<400> 115  
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 ttggtttgtg aatccatctt gctttttccc cattggaact agtcattaac ccatctctga 180  
 actggttagaa aaacatctga agagctagtc tatcagcatc tgacagggtga attggatggt 240  
 tctcagaacc atttcaccca gacagcctgt ttctatcctg ttttaataaat tagtttggtg 300  
 tctctacatg cataacaaac cctgctccaa tctgtcacat aaaagtctgt gacttgaagt 360  
 ttagtc 366

<210> 116  
 <211> 282  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(282)  
 <223> n = A,T,C or G  
 <400> 116  
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 gagaaatgag atnaaacaca atnttataaa gtctacttag agaagatcaa gtgacctcaa 120  
 agactttact attttcatat ttttaagacac atgatttatc ctatttttagt aacctggttc 180  
 atacgttaaa caaaggataa tgtgaacagc agagaggatt tgttggcaga aaatctatgt 240  
 tcaatctnga actatctana tcacagacat ttctattcct tt 282

<210> 117  
 <211> 305  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(305)  
 <223> n = A,T,C or G

<400> 117  
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 aataaggcaa aatatatgaa acaacaggtc tcgagatatt ggaaatcagt caatgaagga 180  
 tactgatccc tgatcactgt cctaatagcag gatgtgggaa acagatgagg tcacctctgt 240  
 gactgccccca gcttactgcc tgtagagagt ttctangctg cagttcagac agggagaaat 300  
 tgggt 305

<210> 118  
 <211> 71  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(71)  
 <223> n = A,T,C or G

<400> 118  
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 aantcctggg t 71

<210> 119  
 <211> 212  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(212)  
 <223> n = A,T,C or G

<400> 119  
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 gaaaatgggg tgaaattggc caactttcta tnaacttatg ttggcaantt tgccaccaac 120  
 agtaagctgg cccttctaataaaaagaaaat tgaaagggtt ctcactaanc ggaattaant 180  
 aatggantca aganactccc aggcctcagc gt 212

<210> 120  
 <211> 90  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(90)  
 <223> n = A,T,C or G

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<210> 121  
<211> 218  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(218)  
<223> n = A,T,C or G

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atatncangt aaattangga atgaattcat ggttcttttg ggaattcctt tacgatngcc 180  
agcatanact tcatgtgggg atancagcta cccttgta 218

<210> 122  
<211> 171  
<212> DNA  
<213> Homo sapien

<400> 122  
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caccaccccg gcggggtcat ctgtgccaca ggtccctgtt gacagtgcgg t 171

<210> 123  
<211> 76  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(76)  
<223> n = A,T,C or G

<400> 123  
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ttatcaanta ttgtgt 76

<210> 124  
<211> 131  
<212> DNA  
<213> Homo sapien

<400> 124  
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caatgtgctg ggtcatatgg aggggaggag actctaaaat agccaatttt attctcttgg 120  
ttaagatttg t 131

<210> 125  
<211> 432  
<212> DNA  
<213> Homo sapien

<400> 125  
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cttgaaaaag aggtgatagc tcttcagagg acttgtgact tttgctcaga tgctgaagaa 120

```

ctacagtctg catttggcag aaatgaagat gaatttggat taaatgagga tgctgaagat    180
ttgcctcacc aaacaaaagt gaaacaactg agagaaaatt ttcaggaaaa aagacagtgg    240
ctcttgaagt atcagtcact tttgagaatg tttcttagtt actgcatact tcatggatcc    300
catggtgggg gtcttgcacg tgtaagaatg gaattgattt tgcttttgca agaattctcag    360
caggaaacat cagaaccact attttctagc cctctgtcag agcaaacctc agtgcctctc    420
ctctttgctt gt                                     432

```

```

<210> 126
<211> 112
<212> DNA
<213> Homo sapien

```

```

<400> 126
acacaacttg aatagtaaaa tagaaactga gctgaaattt ctaattcact ttctaacct    60
agtaagaatg atatttcccc ccagggatca ccaaatattt ataaaaattt gt         112

```

```

<210> 127
<211> 54
<212> DNA
<213> Homo sapien

```

```

<400> 127
accacgaaac cacaacaag atggaagcat caatccactt gccaagcaca gcag         54

```

```

<210> 128
<211> 323
<212> DNA
<213> Homo sapien

```

```

<400> 128
acctcattag taattgtttt gttgtttcat ttttttctaa tgtctcccct ctaccagctc    60
acctgagata acagaatgaa aatggaagga cagccagatt tctcctttgc tctctgctca    120
ttctctctga agtctagggt acccattttg gggaccatt ataggcaata aacacagttc    180
ccaaagcatt tggacagttt cttgttgtgt tttagaatgg ttttcccttt tcttagcctt    240
ttcctgcaaa aggctcactc agtcccttgc ttgctcagtg gactgggctc cccagggcct    300
aggctgcctt cttttccatg tcc                                     323

```

```

<210> 129
<211> 192
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(192)
<223> n = A,T,C or G

```

```

<400> 129
acatacatgt gtgtatattt ttaaatatca cttttgtatc actctgactt tttagcatatc    60
tgaaaacaca ctaacataat ttntgtgaac catgatcaga tacaacccaa atcattcatc    120
tagcacattc atctgtgata naaagatagg tgagtttcat ttccttcacg ttggccaatg    180
gataaacaaa gt                                     192

```

```

<210> 130
<211> 362
<212> DNA
<213> Homo sapien

```

<220>  
 <221> misc\_feature  
 <222> (1)...(362)  
 <223> n = A,T,C or G

<400> 130  
 ccctttttta tggaatgagt agactgtatg tttgaanatt tanccacaac ctctttgaca 60  
 tataatgacg caacaaaaag gtgctgttta gtcctatggt tcagtttatg cccctgacaa 120  
 gtttcatttg tgttttgccg atcttctggc taatcgtggt atcctccatg ttattagtaa 180  
 ttctgtattc cattttgtta acgcctggta gatgtaacct gctangaggc taactttata 240  
 cttattttaa agctcttatt ttgtggtcat taaaatggca atttatgtgc agcactttat 300  
 tgcagcagga agcacgtgtg ggttggttgt aaagctcttt gctaattcta aaaagtaatg 360  
 gg 362

<210> 131  
 <211> 332  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(332)  
 <223> n = A,T,C or G

<400> 131  
 ctttttgaaa gatcgtgtcc actcctgtgg acatcttggt ttaatggagt ttcccatgca 60  
 gtangactgg tatggttgca gctgtccaga taaaaacatt tgaagagctc caaatgaga 120  
 gttctcccag gttcgccctg ctgctccaag tctcagcagc agcctctttt aggaggcatc 180  
 ttctgaacta gattaaggca gcttgtaa atctgtgat ttggtttatt atccaactaa 240  
 cttccatctg ttatcactgg agaaagccca gactcccan gacnggtacg gattgtgggc 300  
 atanaaggat tgggtgaagc tggcgttgtg gt 332

<210> 132  
 <211> 322  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(322)  
 <223> n = A,T,C or G

<400> 132  
 acttttgcca ttttgtatat ataaacaatc ttgggacatt ctctgaaaa ctaggtgtcc 60  
 agtggctaag agaactcgat ttcaagcaat tctgaaagga aaaccagcat gacacagaat 120  
 ctcaaatcc caaacagggg ctctgtggga aaaaatgagg aggacctttg tatctcgggt 180  
 tttagcaagt taaaatgaan atgacaggaa aggcttattt atcaacaaag agaagagttg 240  
 ggatgcttct aaaaaaaact ttggtagaga aaataggaat gctnaatcct aggaagcct 300  
 gtaacaatct acaattgggtc ca 322

<210> 133  
 <211> 278  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(278)

<223> n = A,T,C or G

<400> 133

acaagccttc	acaagttaa	ctaaattggg	attaatcttt	ctgtanttat	ctgcataatt	60
cttggttttc	tttccatctg	gctcctgggt	tgacaatttg	tggaacaac	tctattgcta	120
ctatttataa	aaaatcacia	atctttccct	ttaagctatg	ttnaattcaa	actattcctg	180
ctattcctgt	ttgtcaaag	aaattatatt	tttcaaaata	tgtnatattg	tttgatgggt	240
cccacgaac	actaataaaa	accacagaga	ccagcctg			278

<210> 134

<211> 121

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(121)

<223> n = A,T,C or G

<400> 134

gtttanaaaa	cttgtttagc	tccatagagg	aaagaatggt	aaactttgta	ttttaaaaca	60
tgattctctg	aggttaaact	tggttttcaa	atgttatttt	tacttgtatt	ttgcttttgg	120
t						121

<210> 135

<211> 350

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(350)

<223> n = A,T,C or G

<400> 135

acttanaacc	atgcctagca	catcagaatc	cctcaaagaa	catcagtata	atcctataacc	60
atancaagt	gtgactggtt	aagcgtgcga	caaagggtcag	ctggcacatt	acttgtgtgc	120
aaacttgata	cttttgttct	aagtaggaac	tagtatacag	tncctaggan	tggtactcca	180
gggtgcccc	caactcctgc	agccgctcct	ctgtgccagn	ccctgnaagg	aactttcgtc	240
ccacctcaat	caagccctgg	gccatgctac	ctgcaattgg	ctgaacaaac	gtttgctgag	300
ttcccaagga	tgcaaagcct	ggtgctcaac	tctggtggcg	tcaactcagt		350

<210> 136

<211> 399

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(399)

<223> n = A,T,C or G

<400> 136

tgtaccgtga	agacgacaga	agttgcatgg	cagggacagg	gcagggccga	ggccagggtt	60
gctgtgattg	tatccgaata	ntcctcgtga	gaaaagataa	tgagatgacg	tgagcagcct	120
gcagacttgt	gtctgccttc	anaagccag	acaggaaggc	cctgcctgcc	ttggctctga	180
cctggcggcc	agccagccag	ccacaggtgg	gcttcttcct	tttgtggtga	caacnccaag	240
aaaactgcag	aggcccagg	tcaggtgtna	gtgggtangt	gaccataaaa	caccaggtgc	300

tcccaggaac cccgggcaaag gccatcccca cctacagcca gcatgcccac tggcgtgatg	360
ggtgcagang gatgaagcag ccagntgttc tgctgtggt	399

<210> 137  
 <211> 165  
 <212> DNA  
 <213> Homo sapien  
  
 <220>  
 <221> misc\_feature  
 <222> (1)...(165)  
 <223> n = A,T,C or G

<400> 137	
actggtgtgg tnggggtga tgctggtggt anaagttgan gtgacttcan gatggtgtgt	60
ggaggaagtg tgtgaacgta gggatgtaga ngttttggcc gtgctaaatg agcttcggga	120
ttggctggtc ccactggtgg tcaactgtcat tgggtggggt cctgt	165

<210> 138  
 <211> 338  
 <212> DNA  
 <213> Homo sapien  
  
 <220>  
 <221> misc\_feature  
 <222> (1)...(338)  
 <223> n = A,T,C or G

<400> 138	
actcactgga atgccacatt cacaacagaa tcagaggtct gtgaaaacat taatggctcc	60
ttactttctc cagtaagaat cagggacttg aaatggaaac gttaacagcc acatgcccac	120
tgctgggcag tctcccatgc cttccacagt gaaagggctt gagaaaaatc acatccaatg	180
tcatgtgttt ccagccacac caaaagggtc ttgggggtgga gggctggggg catananggt	240
cangectcag gaagcctcaa gttccattca gctttgccac tgtacattcc ccatntttaa	300
aaaaactgat gccttttttt tttttttttg taaaattc	338

<210> 139  
 <211> 382  
 <212> DNA  
 <213> Homo sapien

<400> 139	
gggaatcttg gtttttgga tctggtttgc ctatagccga ggccactttg acagaacaaa	60
gaaagggact tcagtaaga aggtgattta cagccagcct agtgcccga gtgaaggaga	120
attcaaacag acctcgtcat tctgtgtgtg agcctgggtg gtcaccgcc tatcatctgc	180
atttgctta ctcaggtgct accggactct ggccccgat gtctgtagtt tcacaggatg	240
cettatttgt cttctacacc ccacagggcc ccctacttct tcggatgtgt ttttaataat	300
gtcagctatg tgccccatcc tccttcatgc cctccctccc ttctctacca ctgctgagtg	360
gcctggaact tgtttaaagt gt	382

<210> 140  
 <211> 200  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(200)

<223> n = A,T,C or G

<400> 140

accaaancctt	ctttctgttg	tgtnngattt	tactataggg	gttnngcttn	ttctaaanat	60
acttttcatt	taacancctt	tgtaagtgt	caggtgcac	tttgctccat	anaattattg	120
ttttcacatt	tcaacttgta	tggtttgtc	tcttanagca	ttggtgaaat	cacatatttt	180
atattcagca	taaaggagaa					200

<210> 141

<211> 335

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(335)

<223> n = A,T,C or G

<400> 141

actttatttt	caaaacactc	atatgttgca	aaaaacacat	agaaaaataa	agtttggtgg	60
gggtgctgac	taaacttcaa	gtcacagact	tttatgtgac	agattggagc	agggtttgtt	120
atgcatgtag	agaaccctaaa	ctaatttatt	aaacaggata	gaaacaggct	gtctgggtga	180
aatggttctg	agaaccatcc	aattcacctg	tcagatgctg	atanactagc	tcttcagatg	240
tttttctacc	agttcagaga	tnggttaatg	actanttcca	atggggaaaa	agcaagatgg	300
attcacaaac	caagtaattt	taaacaaaga	cactt			335

<210> 142

<211> 459

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(459)

<223> n = A,T,C or G

<400> 142

accagggttaa	tattgccaca	tatatccttt	ccaattgcgg	gctaaacaga	cgtgtattta	60
gggtgtgtta	aagacaaccc	agcttaatat	caagagaaat	tgtgaccttt	catggagtat	120
ctgatggaga	aaacactgag	ttttgacaaa	tcttatttta	ttcagatagc	agtctgatca	180
cacatgggtcc	aacaacactc	aaataataaa	tcaaatatna	tcagatgtta	aagattggtc	240
ttcaaacatc	atagccaatg	atgccccgct	tgcttataat	ctctccgaca	taaaaccaca	300
tcaaacactc	agtggccacc	aaaccattca	gcacagcttc	cttaactgtg	agctgtttga	360
agctaccagt	ctgagcacta	ttgactatnt	ttttcangct	ctgaatagct	ctagggatct	420
cagcanggggt	gggaggaacc	agctcaacct	tggcgtant			459

<210> 143

<211> 140

<212> DNA

<213> Homo sapien

<400> 143

acatttcctt	ccaccaagtc	aggactcctg	gcttctgtgg	gagttcttat	cacctgaggg	60
aaatccaaac	agtctctcct	agaagggaat	agtgtcacca	acccaccca	tctccctgag	120
accatccgac	ttccctgtgt					140

<210> 144

<211> 164



<212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(164)  
 <223> n = A,T,C or G

<400> 144  
 acttcagtaa caacatacaa taacaacatt aagtgtatat tgccatcttt gtcattttct 60  
 atctatacca ctctcccttc tgaaaacaan aatcactanc caatcactta tacaaatttg 120  
 aggcaattaa tccatatttg ttttcaataa ggaaaaaag atgt 164

<210> 145  
 <211> 303  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(303)  
 <223> n = A,T,C or G

<400> 145  
 acgtagacca tccaactttg tatttgtaat ggcaaacatc cagnagcaat tcctaaacaa 60  
 actggagggt atttataccc aattatccca ttcattaaca tgccctcctc ctccaggctat 120  
 gcaggacagc tatcataagt cggcccaggc atccagatac taccatttgt ataaacttca 180  
 gtaggggagt ccatccaagt gacaggtcta atcaaaggag gaaatggaac ataagcccag 240  
 tagtaaaatn ttgcttagct gaaacagcca caaaagactt accgccgtgg tgattaccat 300  
 caa 303

<210> 146  
 <211> 327  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(327)  
 <223> n = A,T,C or G

<400> 146  
 actgcagctc aattagaagt ggtctctgac tttcatcanc ttctocctgg gctccatgac 60  
 actggcctgg agtgactcat tgctctggtt ggttgagaga gctcctttgc caacaggcct 120  
 ccaagtcagg gctgggattt gtttcctttc cacattctag caacaatatg ctggccactt 180  
 cctgaacagg gagggaggga ggagccagca tggaacaagc tgccactttc taaagtagcc 240  
 agacttgccc ctgggcctgt cacacctact gatgaccttc tgtgcctgca ggatggaatg 300  
 taggggtgag ctgtgtgact ctatggt 327

<210> 147  
 <211> 173  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(173)  
 <223> n = A,T,C or G

&lt;400&gt; 147

acattgtttt tttagataa agcattgana gagctctcct taacgtgaca caatggaagg	60
actggaacac ataccacacat ctttgttctg agggataatt ttctgataaa gtcttgctgt	120
atattcaagc acatatgtta tatattattc agttccatgt ttatagccta gtt	173

&lt;210&gt; 148

&lt;211&gt; 477

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(477)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 148

acaaccactt tatctcatcg aatttttaac ccaaactcac tcaactgtgcc tttctatcct	60
atgggatata ttatttgatg ctccatttca tcacacatat atgaataata cactcatact	120
gccctactac ctgctgcaat aatcacattc ccttcctgtc ctgaccctga agccattggg	180
gtggtcctag tggccatcag tccangcctg caccttgagc ccttgagctc cattgctcac	240
nccanccac ctcaccgacc ccctcctctt acacagctac ctcttgctc tctaaccca	300
tagattatnt ccaaattcag tcaattaagt tactattaac actctaccg acatgtccag	360
caccactggt aagccttctc cagccaacac acacacacac acacncacac acacacatat	420
ccaggcacag gctacctcat cttcacaatc acccctttaa ttaccatgct atggtgg	477

&lt;210&gt; 149

&lt;211&gt; 207

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 149

acagttgtat tataatatca agaaataaac ttgcaatgag agcatttaag agggaagaac	60
taacgtatth tagagagcca aggaaggtht ctgtggggag tgggatgtaa ggtggggcct	120
gatgataaat aagagtcagc caggtaagtg ggtggtgtgg tatgggcaca gtgaagaaca	180
tttcaggcag agggaacagc agtgaaa	207

&lt;210&gt; 150

&lt;211&gt; 111

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(111)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 150

accttgatth cattgctgct ctgatggaaa cccaactatc taatttagct aaaacatggg	60
cacttaaatg tggtcagtgt ttggacttgt taactantgg catctttggg t	111

&lt;210&gt; 151

&lt;211&gt; 196

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 151

agcgcgagc gtcattattga acattccaga tacctatcat tactcgatgc tgttgataac	60
---	----

agcaagatgg ctttgaactc agggtcacca ccagctattg gaccttacta tgaaaaccat	120
ggataccaac cggaaaaccc ctatcccga cagccactg tggatcccccac tgtctacgag	180
gtgcatccgg ctcaagt	196

<210> 152  
 <211> 132  
 <212> DNA  
 <213> Homo sapien

<400> 152	
acagcacttt cacatgtaag aaggagaaaa ttccctaaatg taggagaaaag ataacagAAC	60
cttccccttt tcatctagtgt gtggaacact gatgctttat gttgacagga atagaaccag	120
gaggagattt gt	132

<210> 153  
 <211> 285  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(285)  
 <223> n = A,T,C or G

<400> 153	
acaanaccca nganaggcca ctggccgtgg tgtcatggcc tccaaacatg aaagtgtcag	60
cttctgctct tatgtcctca tctgacaact ctttaccatt tttatcctcg ctcagcagga	120
gcacatcaat aaagtccaaa gtcttgact tggccttggc ttggaggaag tcatcaacac	180
cctggctagt gaggtgctgg cgccgtcctt ggatgacggc atctgtgaag tctgtcacca	240
gtctgcaggc cctgtggaag cgccgtccac acggagtnag gaatt	285

<210> 154  
 <211> 333  
 <212> DNA  
 <213> Homo sapien

<400> 154	
accacagtcc tgttgggcca gggtttcatg accctttctg tgaaaagcca tattatcacc	60
accccaatt tttccttaaa tatctttaac tgaaggggtc agcctcttga ctgcaaagac	120
cctaagccgg ttacacagct aactccact ggccctgatt tgtgaaattg ctgctgcctg	180
attggcacag gactcgaagg tttcagctc ccctcctccg tggaacgaga ctctgatttg	240
agtttcacaa attctcgggc cacctcgtca ttgtcctctt gaaataaaat ccggagaatg	300
gtcaggcctg tctcatccat atggatcttc cgg	333

<210> 155  
 <211> 308  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(308)  
 <223> n = A,T,C or G

<400> 155	
actggaaata ataaaaccca catcacagtgt ttgtgtcaaa gatcatcagg gcatggatgg	60
gaaagtgcctt tgggaactgt aaagtgccta acacatgatc gatgattttt gttataatat	120
ttgaatcacg gtgcatacaa actctcctgc ctgctcctcc tgggccccag cccagcccc	180

atcacagctc actgctctgt tcatccaggc ccagcatgta gtggtgatt cttcttggt	240
gcttttagcc tccanaagtt tctctgaagc caaccaaacc tctangtgta aggcattgtg	300
gccctggg	308

<210> 156  
 <211> 295  
 <212> DNA  
 <213> Homo sapien

<400> 156	
accttgctcg gtgcttgaa catattagga actcaaaata tgagatgata acagtgccta	60
ttattgatta ctgagagaac tgtagacat ttagttgaag attttctaca caggaactga	120
gaataggaga ttatgtttgg ccctcatatt ctctcctatc ctcttgctt cattctatgt	180
ctaataatatt ctcaatcaaa taaggtagc ataatcagga aatcgaccaa ataccaatat	240
aaaaccagat gtctatcctt aagattttca aatagaaaac aaattaacag actat	295

<210> 157  
 <211> 126  
 <212> DNA  
 <213> Homo sapien

<400> 157	
acaagtttaa atagtgtgt cactgtgcat gtgctgaaat gtgaaatcca ccacatttct	60
gaagagcaaa acaaattctg tcatgtaatc tctatcttgg gtcgtgggta tatctgtccc	120
cttagt	126

<210> 158  
 <211> 442  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(442)  
 <223> n = A,T,C or G

<400> 158	
accactgggt cttggaaaca cccatcctta atacgatgat ttttctgtcg tgtgaaaatg	60
aanccagcag gctgccccta gtcagtcctt ccttccagag aaaaagagat ttgagaaagt	120
gcctgggtaa ttcaccatta atttcctccc ccaaactctc tgagtcttcc cttaatattt	180
ctggtggttc tgaccaaagc aggtcatggt ttgttgagca tttgggatcc cagtgaagta	240
natgtttgta gccttgcata cttagccctt cccacgcaca aacggagtgg cagagtgggtg	300
ccaaccctgt tttccagtc cacgtagaca gattcacagt gcggaattct ggaagctgga	360
nacagacggg ctctttgcag agccgggact ctgagangga catgagggcc tctgcctctg	420
tgttcattct ctgatgtcct gt	442

<210> 159  
 <211> 498  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(498)  
 <223> n = A,T,C or G

<400> 159	
acttcagggt aacgttggtg tttccgttga gcctgaactg atgggtgacg ttgtaggttc	60

tccaacaaga	actgaggttg	cagagcgggt	agggagaggt	gctgttccag	ttgcacctgg	120
gctgctgtgg	actgttggtg	attcctcact	acggcccaag	gttgtggaac	tggcanaaag	180
gtgtgtgtgt	gganttgagc	tcgggcggct	gtggtaggtt	gtgggctctt	caacaggggc	240
tgctgtggtg	ccgggangtg	aangtgttgt	gtcacttgag	cttggccagc	tctggaaagt	300
antanattct	tcctgaaggc	cagcgcttgt	ggagctggca	ngggtcantg	ttgtgtgtaa	360
cgaaccagtg	ctgctgtggg	tgggtgtana	tcctccacaa	agcctgaagt	tatgggtgtcn	420
tcaggtanaa	atgtggtttc	agtgtccctg	ggcngctgtg	gaaggttgta	nattgtcacc	480
aagggaataa	gctgtggt					498

&lt;210&gt; 160

&lt;211&gt; 380

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(380)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 160

acctgcatcc	agcttccctg	ccaaactcac	aaggagacat	caacctctag	acagggaaac	60
agcttcagga	tacttccagg	agacagagcc	accagcagca	aaacaaatat	tcccatgcct	120
ggagcatggc	atagaggaag	ctganaaatg	tggggtctga	ggaagccatt	tgagtctggc	180
cactagacat	ctcatcagcc	acttgtgtga	agagatgccc	catgacccca	gatgcctctc	240
ccacccttac	ctccatctca	cacacttgag	ctttccactc	tgtataattc	taacatcctg	300
gagaaaaatg	gcagtttgac	cgaacctgtt	cacaacggta	gaggctgatt	tctaacgaaa	360
cttgtagaat	gaagcctgga					380

&lt;210&gt; 161

&lt;211&gt; 114

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 161

actccacatc	ccctctgagc	aggcggttgt	cgttcaaggt	gtatttggcc	ttgcctgtca	60
cactgtccac	tggcccctta	tccacttggt	gcttaatccc	tcgaaagagc	atgt	114

&lt;210&gt; 162

&lt;211&gt; 177

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 162

actttctgaa	tcgaatcaaa	tgatacttag	tgtagtttta	atatacctcat	atatatcaaa	60
gttttactac	tctgataatt	ttgtaaacca	ggtaaccaga	acatccagtc	atacagcttt	120
tggtgatata	taacttggca	ataaccagct	ctggtgatac	ataaaaactac	tcactgt	177

&lt;210&gt; 163

&lt;211&gt; 137

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(137)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 163

catttataca gacaggcgtg aagacattca cgacaaaaac gcgaaattct atcccgtgac	60
canagaaggc agctacggct actcctacat cctggcgtgg gtggccttcg cctgcacctt	120
catcagcggc atgatgt	137

&lt;210&gt; 164

&lt;211&gt; 469

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(469)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 164

cttatcacaa tgaatgttct cctgggcagc gttgtgatct ttgccacctt cgtgacttta	60
tgcaatgcat catgctatct cctacctaata gagggagttc caggagattc aaccaggaaa	120
tgcatggatc tcaaaggaaa caaacaccca ataaactcgg agtggcagac tgacaactgt	180
gagacatgca cttgctacga aacagaaatt tcatgttgca cccttgtttc tacacctgtg	240
ggttatgaca aagacaactg ccaaagaatc ttcaagaagg aggactgcaa gtatatcgtg	300
gtggagaaga aggaccctaa aaagacctgt tctgtcagtg aatggataat ctaatgtgct	360
tctagtaggc acagggtccc caggccaggc ctcatctcc tctggcctct aatagtcaat	420
gattgtgtag ccatgcctat cagtaaaaag atntttgagc aaacacttt	469

&lt;210&gt; 165

&lt;211&gt; 195

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(195)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 165

acagtttttt atanatatcg acattgccgg cacttgtgtt cagtttcata aagctgggtg	60
atccgctgtc atccactatt ccttggctag agtaaaaatt attcttatag cccatgtccc	120
tgcaggccgc ccgcccgtag ttctcgttcc agtcgtcttg gcacacaggg tgccaggact	180
tcctctgaga tgagt	195

&lt;210&gt; 166

&lt;211&gt; 383

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(383)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 166

acatcttagt agtgtggcac atcagggggc catcagggtc acagtcactc atagcctcgc	60
cgaggctcga gtccacacca ccgggtgtagg tgtgtcctaat cttgggcttg gcgcccacct	120
ttggagaagg gatatgctgc acacacatgt ccacaaagcc tgtgaactcg ccaaagaatt	180
tttgacagacc agcctgagca agggggcgat gtccagcttc agctcctct tccgtcagggtg	240
gatgcccaacc tcgtctangg tccgtgggaa gctgggtgtc acntcaccta caacctgggc	300
gangatctta taaagaggct ccnagataaa ctccacgaaa cttctctggg agctgctagt	360
nggggccttt ttggtgaact ttc	383

<210> 167  
 <211> 247  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(247)  
 <223> n = A,T,C or G

<400> 167  
 acagagccag accttgGCCa taaatgaanc agagattaag actaaacccc aagtcganat 60  
 tggagcagaa actggagcaa gaagtgggcc tggggctgaa gtagagacca aggccactgc 120  
 tatanccata cacagagcca actctcaggc caaggcnatg gttggggcag anccagagac 180  
 tcaatctgan tccaaagtgg tggctggaac actggctcatg acanaggcag tgactctgac 240  
 tgangtc 247

<210> 168  
 <211> 273  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(273)  
 <223> n = A,T,C or G

<400> 168  
 acttctaagt tttctagaag tggaaggatt gtantcatcc tgaaaatggg tttacttcaa 60  
 aatccctcan ccttgttctt cacnactgtc tatactgana gtgtcatgtt tccacaaagg 120  
 gctgacacct gagcctgnat tttactcat ccctgagaag ccctttccag taggggtggc 180  
 aattccaac ttccttgcca caagcttccc aggccttctc ccctggaaaa ctccagcttg 240  
 agtcccagat acactcatgg gctgccctgg gca 273

<210> 169  
 <211> 431  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(431)  
 <223> n = A,T,C or G

<400> 169  
 acagccttgg cttccccaaa ctccacagtc tcagtgcaga aagatcatct tccagcagtc 60  
 agctcagacc aggggtcaaag gatgtgacat caacagtttc tggtttcaga acaggttcta 120  
 ctactgtcaa atgaccccc atacttcctc aaaggctgtg gtaagttttg cacaggtgag 180  
 ggcagcagaa agggggtant tactgatgga caccatcttc tctgtatact ccacactgac 240  
 cttgccatgg gcaaaggccc ctaccacaaa aacaatagga tcaactgctgg gcaccagtc 300  
 acgcacatca ctgacaaccg ggatggaaaa agaantgcc aactttcatac atccaactgg 360  
 aaagtgatct gatactggat tcttaattac cttcaaaagc ttctgggggc catcagctgc 420  
 tcgaacactg a 431

<210> 170  
 <211> 266  
 <212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(266)

<223> n = A,T,C or G

<400> 170

acctgtgggc	tggtctgtta	tgctgtgcc	ggctgtgaa	agggagttca	gaggtggagc	60
tcaaggagct	ctgcaggcat	tttgccaanc	ctctccanag	canagggagc	aacctacact	120
ccccgctaga	aagacaccag	attggagtcc	tgggaggggg	agttgggggtg	ggcatttgat	180
gtatacttgt	cacctgaatg	aangagccag	agaggaanga	gacgaanatg	anattggcct	240
tcaaagctag	gggtctggca	ggtgga				266

<210> 171

<211> 1248

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(1248)

<223> n = A,T,C or G

<400> 171

ggcagccaaa	tcataaacgg	cgaggactgc	agcccgcact	cgagccctg	gcaggcggca	60
ctggtcatgg	aaaacgaatt	gttctgctcg	ggcgtcctgg	tgcatccgca	gtgggtgctg	120
tcagccgcac	actgtttcca	gaagtgagtg	cagagctcct	acaccatcgg	gctgggcctg	180
cacagtcttg	aggccgacca	agagccaggg	agccagatgg	tggaggccag	cctctccgta	240
cggcacccag	agtacaacag	acccttgctc	gctaaccgacc	tcagtctcat	caagttggac	300
gaatccgtgt	ccgagtctga	caccatccgg	agcatcagca	ttgcttcgca	gtgccctacc	360
gcggggaact	cttgccctcg	ttctggctgg	ggtctgctgg	cgaacggcag	aatgcctacc	420
gtgctgcagt	gcgtgaacgt	gtcggtggtg	tctgaggagg	tctgcagtaa	gctctatgac	480
ccgctgtacc	accccgagcat	gttctgcgcc	ggcggagggc	aagaccagaa	ggactcctgc	540
aacggtgact	ctgggggggc	cctgatctgc	aacgggtact	tgagggcct	tgtgtctttc	600
ggaaaagccc	cgtgtggcca	agttggcgtg	ccaggtgtct	acaccaaact	ctgcaaattc	660
actgagtggg	tagagaaaac	cgtccaggcc	agttaactct	ggggactggg	aaccatgaa	720
attgaccccc	aaatacatcc	tgcggaagga	attcaggaat	atctgttccc	agccctcct	780
ccctcaggcc	caggagtcca	ggccccagc	ccctcctccc	tcaaaccaag	ggtacagatc	840
cccagccct	cctccctcag	accagaggat	ccagaccccc	cagccctccc	tccctcagac	900
ccaggagtcc	agccctcct	ccctcagacc	caggagtcca	gacccccag	cccctcctcc	960
ctcagaccga	gggtccagg	cccccaacc	ctcctccctc	agactcagag	gtccaagccc	1020
ccaacccttc	attcccaga	cccagaggtc	caggtcocag	ccctctntcc	ctcagaccga	1080
gcggtccaat	gccacctaga	ctntccctgt	acacagtgcc	cccttggtggc	acgttgaccc	1140
aaccttacca	gttggttttt	catttttngt	ccctttcccc	tagatccaga	aataaagttt	1200
aagagaagng	caaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa		1248

<210> 172

<211> 159

<212> PRT

<213> Homo sapien

<220>

<221> VARIANT

<222> (1)...(159)

<223> Xaa = Any Amino Acid

<400> 172



```

Met Val Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro
 1           5           10           15
Leu Leu Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser
           20           25           30
Glu Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr
           35           40           45
Ala Gly Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly
 50           55           60
Arg Met Pro Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu
 65           70           75           80
Glu Val Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe
           85           90           95
Cys Ala Gly Gly Gly Gln Xaa Gln Xaa Asp Ser Cys Asn Gly Asp Ser
           100          105          110
Gly Gly Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe
           115          120          125
Gly Lys Ala Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn
           130          135          140
Leu Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
145           150           155

```

&lt;210&gt; 173

&lt;211&gt; 1265

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(1265)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 173

```

ggcagccgcg actgcagcc ctggcaggcg gcactgggtca tggaaaacga attgttctgc      60
tcgggcgtcc tgggtgcatcc gcagtgggtg ctgtcagccg cacactgttt ccagaactcc      120
tacaccatcg ggctgggcct gcacagtctt gaggccgacc aagagccagg gagccagatg      180
gtggaggcca gcctctccgt acggcaccca gagtacaaca gaccttgct cgctaacgac      240
ctcatgctca tcaagttgga cgaatccgtg tccgagtctg acaccatccg gagcatcagc      300
attgcttcgc agtgccttac cgcggggaac tcttgctctg tttctggctg gggctctgtg      360
gcgaacggtg agctcacggg tgtgtgtctg ccctcttcaa ggaggtcctc tgcccagtcg      420
cgggggctga ccagagctc tgcgtcccag gcagaatgcc taccgtgctg cagtgcgtga      480
acgtgtcggg ggtgtctgag gaggtctgca gtaagctcta tgaccgcgtg taccaccca      540
gcatgttctg cgcggcgga gggcaagacc agaaggactc ctgcaacggt gactctgggg      600
ggcccctgat ctgcaacggg tacttgagg gccttgtgtc ttctggaaaa gcccgtgtg      660
gccaaagtgg cgtgccagggt gtctacacca acctctgcaa attcactgag tggatagaga      720
aaaccgtcca ggccagttaa ctctggggac tgggaacca tgaaattgac ccccaaatac      780
atcctgcgga aggaattcag gaatatctgt tcccagcccc tcctccctca ggcccaggag      840
tccaggcccc cagcccctcc tccctcaaac caagggtaca gatccccagc ccctcctccc      900
tcagaccagc gagtccagac cccccagccc ctctccctc agaccagga gtccagcccc      960
tcctccntca gaccaggag tccagacccc ccagcccctc ctccctcaga cccaggggtt     1020
gaggccccc acccctcctc ctccagagtc agaggtccaa gcccacaacc cctcgttccc     1080
cagaccaga cgttnnaggtc ccagcccctc ttccntcaga ccagnggtc caatgccacc     1140
tagattttcc ctgnacacag tgcccccttg tggngangttg acccaacctt accagttggt     1200
ttttcatttt tngtcccttt cccctagatc cagaaataaa gtttaagaga ngngcaaaaa     1260
aaaaa                                           1265

```

&lt;210&gt; 174

&lt;211&gt; 1459

&lt;212&gt; DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(1459)

<223> n = A,T,C or G

<400> 174

ggtcagccgc	acactgtttc	cagaagtgc	tgacagctc	ctacaccatc	gggtggggcc	60
tgacagctc	tgaggccgac	caagagccag	ggagccagat	gggtggaggcc	agcctctccg	120
tacggcacc	agagtacaac	agacccttgc	tcgctaacga	cctcatgctc	atcaagttgg	180
acgaatccgt	gtccgagtct	gacaccatcc	ggagcatcag	cattgcttcg	cagtgcctta	240
ccgcggggaa	ctcttgccct	gtttctggct	gggtctgct	ggcgaacggg	gagctcacgg	300
gtgtgtgtct	gccctcttca	aggaggtcct	ctgcccagtc	gcgggggctg	acccagagct	360
ctgcgtccca	ggcagaatgc	ctaccgtgct	gcagtgcgtg	aacgtgtcgg	tgggtgtctga	420
ngaggtctgc	antaagctct	atgaccgct	gtaccacccc	ancatgttct	gcgcggcg	480
agggcaagac	cagaaggact	cctgcaacgt	gagagagggg	aaaggggagg	gcaggcgact	540
caggggaagg	tggagaagg	ggagacagag	acacacaggg	ccgcatggcg	agatgcagag	600
atggagagac	acacagggag	acagtgacaa	ctagagagag	aaactgagag	aaacagagaa	660
ataaacacag	gaataaagag	aagcaaagga	agagagaaac	agaaacagac	atggggaggc	720
agaaacacac	acacatagaa	atgcagttga	ccttccaaca	gcatggggcc	tgagggcggg	780
gacctccacc	caatagaaaa	tcctcttata	acttttgact	ccccaaaaac	ctgactagaa	840
atagcctact	gttgacgggg	agccttacca	ataacataaa	tagtcgattt	atgcatacgt	900
tttatgcatt	catgatatac	ctttgttga	attttttgat	atttctaagc	tacacagttc	960
gtctgtgaat	ttttttaaat	tggtgcaact	ctcctaaaat	ttttctgatg	tgtttattga	1020
aaaaatccaa	gtataagtgg	acttgtgcat	tcaaaccagg	gttgttcaag	ggtcaactgt	1080
gtaccagag	ggaaacagt	acacagattc	atagaggtga	aaacgaaga	gaaacaggaa	1140
aatcaagac	tctacaaaga	ggctgggcag	ggtggctcat	gcctgtaatc	ccagcacttt	1200
gggaggcgag	gcaggcagat	cacttgaggt	aaggagttca	agaccagcct	ggccaaaatg	1260
gtgaaatcct	gtctgtacta	aaaatacaaa	agttagctgg	atatgggtgg	aggcgctgt	1320
aatcccagct	acttgggagg	ctgaggcagg	agaattgctt	gaatatggga	ggcagaggtt	1380
gaagtgaagt	gagatcacac	cactatactc	cagctggggc	aacagagtaa	gactctgtct	1440
caaaaaaaaa	aaaaaaaaa					1459

<210> 175

<211> 1167

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(1167)

<223> n = A,T,C or G

<400> 175

gcgcagccct	ggcaggcggc	actggtcatg	gaaaacgaat	tggtctgctc	gggcgtcctg	60
gtgcatccgc	agtgggtgct	gtcagccgca	cactgtttcc	agaactccta	caccatcggg	120
ctgggcctgc	acagtcttga	ggccgaccaa	gagccaggga	gccagatggg	ggaggccagc	180
ctctccgtac	ggcaccaga	gtacaacaga	ctcttgctcg	ctaacgacct	catgtctcatc	240
aagttggagc	aatccgtgtc	cgagtctgac	accatccgga	gcatcagcat	tgcttcgcag	300
tgccctaccg	cggggaactc	ttgcctcgtn	tctggctggg	gtctgctggc	gaacggcaga	360
atgcctaccg	tgctgcactg	cgtgaacgtg	tcggtgggtg	ctgaggangt	ctgcagtaag	420
ctctatgacc	cgctgtacca	ccccagcatg	ttctgcgcgg	gcggagggca	agaccagaag	480
gactcctgca	acggtgactc	tggggggccc	ctgatctgca	acgggtactt	gcagggcctt	540
gtgtctttcg	gaaaagcccc	gtgtggccaa	cttggcgtgc	caggtgtcta	caccaacctc	600
tgcaaattca	ctgagtggat	agagaaaacc	gtccagncca	gttaactctg	gggactggga	660
acccatgaaa	ttgaccccca	aatacatcct	gcggaangaa	ttcaggaata	tctgttccca	720
gcccctcctc	cctcaggccc	aggagtccag	gccccagcc	cctcctccct	caaaccaagg	780

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gtacagatcc ccagcccctc ctccctcaga cccaggagtc cagacccccc agcccctcnt      840
ccntcagacc caggagtcca gcccctcctc cntcagacgc aggagtccag acccccacgc      900
ccntcntccg tcagaccacg ggggtgcaggc ccccaacccc tcntccntca gagtcagagg      960
tccaagcccc caaccctcg ttccccagac ccagaggtnc aggtcccage ccctcctccc      1020
tcagaccacg cggccaatg ccacctagan tntccctgta cacagtgcc ccttgtggca      1080
ngttgaccca accttaccag ttggtttttc attttttgtc cctttccctc agatccagaa      1140
ataaagtnta agagaagcgc aaaaaaa      1167

```

&lt;210&gt; 176

&lt;211&gt; 205

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; (1)...(205)

&lt;223&gt; Xaa = Any Amino Acid

&lt;400&gt; 176

```

Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln Trp
 1          5          10          15
Val Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu
          20          25          30
Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val
          35          40          45
Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Leu Leu Leu
          50          55          60
Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser
          65          70          75          80
Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly
          85          90          95
Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg Met
          100          105          110
Pro Thr Val Leu His Cys Val Asn Val Ser Val Val Ser Glu Xaa Val
          115          120          125
Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys Ala
          130          135          140
Gly Gly Gly Gln Asp Gln Lys Asp Ser Cys Asn Gly Asp Ser Gly Gly
          145          150          155          160
Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly Lys
          165          170          175
Ala Pro Cys Gly Gln Leu Gly Val Pro Gly Val Tyr Thr Asn Leu Cys
          180          185          190
Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Xaa Ser
          195          200          205

```

&lt;210&gt; 177

&lt;211&gt; 1119

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 177

```

gcgcactcgc agccctggca ggccggcactg gtcattgaaa acgaattggt ctgctcgggc      60
gtcctggtgc atccgcagtg ggtgctgtca gccgcacact gtttcagaa ctcctacacc      120
atcgggctgg gcctgcacag tcttgaggcc gaccaagagc cagggagcca gatggtggag      180
gccagcctct ccgtacggca cccagagtac aacagaccct tgctcgctaa cgacctcatg      240
ctcatcaagt tggacgaatc cgtgtccgag tctgacacca tccggagcat cagcattgct      300
tcgcagtgcc ctaccgcggg gaactcttgc ctcttttctg gctggggtct gctggcgaac      360

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gatgctgtga ttgccatcca gtcccagact gtgggaggct gggagtgtga gaagctttcc 420
caaccctggc aggggtgtac catttcggca acttccagtg caaggacgtc ctgctgcatc 480
ctcactgggt gctcactact gctcactgca tcacccgga cactgtgatc aactagccag 540
caccatagtt ctccgaagtc agactatcat gattactgtg ttgactgtgc tgtctattgt 600
actaaccatg ccgatgttta ggtgaaatta gcgtcacttg gcctcaacca tcttggtatc 660
cagttatcct cactgaattg agatttcctg cttcagtgtc agccattccc acataatttc 720
tgacctacag aggtgagggg tcatatagct cttcaaggat gctgggtactc ccctcacaaa 780
ttcattttctc ctggtgtagt gaaagggtgc ccctctggag cctcccaggg tgggtgtgca 840
ggtcacaatg atgaatgtat gatcgtgttc ccattaccca aagcctttaa atccctcatg 900
ctcagtacac cagggcaggt ctagcatttc ttcatttagt gtatgctgtc cattcatgca 960
accacctcag gactcctgga ttctctgcct agttgagctc ctgcatgctg cctccttggg 1020
gaggtgaggg agagggccca tggttcaatg ggatctgtgc agttgtaaca cattaggtgc 1080
ttaataaaca gaagctgtga tgttaaaaaa aaaaaaaaa 1119

```

<210> 178  
 <211> 164  
 <212> PRT  
 <213> Homo sapien

<220>  
 <221> VARIANT  
 <222> (1)...(164)  
 <223> Xaa = Any Amino Acid

<400> 178

```

Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln Trp
1      5      10      15
Val Leu Ser Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu
20     25     30
Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val
35     40     45
Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu Leu
50     55     60
Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser
65     70     75     80
Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly
85     90     95
Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Asp Ala Val
100    105    110
Ile Ala Ile Gln Ser Xaa Thr Val Gly Gly Trp Glu Cys Glu Lys Leu
115    120    125
Ser Gln Pro Trp Gln Gly Cys Thr Ile Ser Ala Thr Ser Ser Ala Arg
130    135    140
Thr Ser Cys Cys Ile Leu Thr Gly Cys Ser Leu Leu Leu Thr Ala Ser
145    150    155    160
Pro Gly Thr Leu

```

<210> 179  
 <211> 250  
 <212> DNA  
 <213> Homo sapien

<400> 179

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ctggagtgcc ttggtgtttc aagcccctgc aggaagcaga atgcaccttc tgaggcacct 60
ccagctgccc ccggccgggg gatgcgaggc tcggagcacc cttgcccggc tgtgattgct 120
gccaggcact gttcatctca gcttttctgt ccctttgctc ccggcaagcg cttctgtga 180
aagttcatat ctggagcctg atgtcttaac gaataaaggt cccatgctcc acccgaaaaa 240

```

aaaaaaaaa 250

<210> 180  
 <211> 202  
 <212> DNA  
 <213> Homo sapien

<400> 180  
 actagtccag tgtggtggaa ttccattgtg ttggggcccaa cacaatgggt acctttaaca 60  
 tcacccagac cccgcccctg cccgtgcccc acgctgctgc taacgacagt atgatgctta 120  
 ctctgtact cggaactat ttttatgtaa ttaatgtatg ctttcttgtt tataaatgcc 180  
 tgatttaaaa aaaaaaaaaa aa 202

<210> 181  
 <211> 558  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(558)  
 <223> n = A,T,C or G

<400> 181  
 tccytttgkt naggtttkkg agacamceck agacctwaan ctgtgtcaca gacttcyngg 60  
 aatgtttagg cagtgttagt aatttcytcg taatgattct gttattactt tcctnattct 120  
 ttattcctct ttcttctgaa gattaatgaa gttgaaaatt gaggtggata aatacaaaaa 180  
 ggtagtgtga tagtataagt atctaagtgc agatgaaagt gtgttatata tatccattca 240  
 aaattatgca agttagtaat tactcagggt taactaaatt actttaatat gctgttgaaac 300  
 ctactctgtt ccttggttag aaaaaattat aaacaggact ttgttagttt gggaagccaa 360  
 attgataata ttctatgttc taaaagttgg gctatacata aattattaag aaatatggaw 420  
 ttttattccc aggaatatgg kgttcatttt atgaatatta cscrggatag awgtwtgagt 480  
 aaaaycagtt ttggtwaata ygtwaatatg tcmtaaataa acaakgcttt gacttatttc 540  
 caaaaaaaaa aaaaaaaaaa 558

<210> 182  
 <211> 479  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(479)  
 <223> n = A,T,C or G

<400> 182  
 acagggwttk grggatgcta agsccccrga rwtggtttga tccaaccctg gcttwttttc 60  
 agaggggaaa atggggccta gaagttacag mscatytagy tgggtgcmgtg gcacccctgg 120  
 cstcacacag astcccagat agctgggact acaggcacac agtcactgaa gcaggccctg 180  
 ttwgcaattc acgttgccac ctccaactta aacattcttc atatgtgatg tccttagtca 240  
 ctaaggttaa actttccac ccagaaaagg caacttagat aaaatcttag agtactttca 300  
 tactmttcta agtcctcttc cagcctcact kkgagtctm cytgggggtt gataggaant 360  
 ntctcttggc tttctcaata aartctctat ycatctcatg ttttaatttg tacgcata 420  
 awtgstgata aaattaaaat gttctggtty mactttaaaa aaaaaaaaaa aaaaaaaaaa 479

<210> 183  
 <211> 384  
 <212> DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 183

aggcgaggagc	agaagctaaa	gccaaagccc	aagaagagtg	gcagtgccag	cactgggtgcc	60
agtaccagta	ccaataacag	tgcagtgcc	agtgccagca	ccagtgggtg	cttcagtgtc	120
ggtgccagcc	tgaccgccac	tctcacattt	gggtctctcg	ctggccttgg	tggagctggt	180
gccagcacca	gtggcagctc	tggtgcctgt	ggtttctcct	acaagtgaga	ttttagatat	240
tggttaatcct	gccagtcttt	ctcttcaagc	caggggtgcat	cctcagaaac	ctactcaaca	300
cagcactcta	ggcagccact	atcaatcaat	tgaagttgac	actctgcatt	aratctattt	360
gccattttcaa	aaaaaaaaaa	aaaa				384

&lt;210&gt; 184

&lt;211&gt; 496

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(496)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 184

accgaattgg	gaccgctggc	ttataagcga	tcatgttynt	ccrgtatcac	ctcaacgagc	60
aggagatcg	agtctatacg	ctgaagaaat	ttgaccgat	gggacaacag	acctgctcag	120
cccacctgc	tcggttctcc	ccagatgaca	aatactctsg	acaccgaatc	accatcaaga	180
aacgcttcaa	ggtgctcatg	accagcaac	cgccgctgt	cctctgaggg	tcccttaaac	240
tgatgtcttt	tctgccacct	gttacccttc	ggagactccg	taaccaaact	cttcggactg	300
tgagccctga	tgcttttttg	ccagccatac	tctttggcat	ccagtctctc	gtggcgattg	360
attatgcttg	tgtgaggcaa	tcatggtggc	atcacccata	aagggaaacac	atttgacttt	420
ttttctctcat	attttaaatt	actacmagaw	tattwmagaw	waaatgawtt	gaaaaactst	480
taaaaaaaaa	aaaaaa					496

&lt;210&gt; 185

&lt;211&gt; 384

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 185

gctggtagcc	tatggcgkkg	cccacggagg	ggctcctgag	gccacggrac	agtgacttcc	60
caagtatcyt	gcgcsgcgtc	ttctaccgtc	cctacctgca	gatcttcggg	cagattcccc	120
aggaggacat	ggacgtggcc	ctcatggagc	acagcaactg	ytcgctcgag	cccggtctct	180
gggcacaccc	tccctggggc	caggcgggca	cctgcgtctc	ccagtatgcc	aactggctgg	240
tggtgctgct	cctcgctcatc	ttcctgctcg	tgccaacat	cctgctggtc	aacttgctca	300
ttgccatggt	cagttacaca	ttcggaag	tacagggcaa	cagcgatctc	tactgggaag	360
gcgcagcggt	accgcctcat	ccgg				384

&lt;210&gt; 186

&lt;211&gt; 577

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(577)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 186

gagttagctc	ctccacaacc	ttgatgaggt	cgtctgcagt	ggcctctcgc	ttcataccgc	60
------------	------------	------------	------------	------------	------------	----

tnccatcgtc	atactgtagg	tttgccacca	cytcctggca	tcttggggcg	gcntaatatt	120
ccaggaaact	ctcaatcaag	tcaccgtcga	tgaacctgt	gggctgggtc	tgtcttccgc	180
tcggtgtgaa	aggatctccc	agaaggagt	ctcgatcttc	cccacacttt	tgatgacttt	240
attgagtcga	ttctgcatgt	ccagcaggag	gttgtaccag	ctctctgaca	gtgagggtcac	300
cagccctatc	atgccgttga	mcgtgccgaa	garcaccgag	ccttgtgtgg	gggkkgaagt	360
ctcaccacaga	ttctgcatta	ccagagagcc	gtggcaaaa	acattgacaa	actcgcccag	420
gtggaaaaag	amcamctcct	ggargtgctn	gccgctcttc	gtcmgttgg	ggcagcgctw	480
tccttttgac	acacaaacaa	gttaaaggca	ttttcagccc	ccagaaantt	gtcatcatcc	540
aagatntcgc	acagcactna	tccagttggg	attaaat			577

&lt;210&gt; 187

&lt;211&gt; 534

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(534)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 187

aacatcttcc	tgtataatgc	tgtgtaatat	cgatccgatn	ttgtctgstg	agaatycatw	60
actkggaaaa	gmaacattaa	agcctggaca	ctggtattaa	aattcacaa	atgcaacact	120
ttaaacagtg	tgtcaatctg	ctcccyynac	tttgcataca	ccagtctggg	aakaagggta	180
tgccctattc	acacctgtta	aaagggcgct	aagcattttt	gattcaacat	cttttttttt	240
gacacaagtc	cgaaaaaagc	aaaagtaaac	agttatyaat	ttgttagcca	attcactttc	300
ttcatgggac	agagccatyt	gatttaaaaa	gcaaattgca	taatattgag	cttygggagc	360
tgatatttga	gcggaagagt	agcctttcta	cttcaccaga	cacaactccc	tttcatattg	420
ggatgttnac	naaagtwatg	tctctwacag	atgggatgct	tttgtggcaa	ttctgttctg	480
aggatctccc	agtttatitta	ccacttgcac	aagaaggcgt	tttcttcttc	aggc	534

&lt;210&gt; 188

&lt;211&gt; 761

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(761)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 188

agaaaccagt	atctctnaaa	acaacctctc	ataccttggt	gacctaat	ttgtgtgcgtg	60
tgtgtgtgcg	cgcatattat	atagacaggc	acatcttttt	tacttttgta	aaagcttatg	120
cctctttggt	atctatatct	gtgaaagttt	taatgatctg	ccataatgtc	ttggggacct	180
ttgtcttctg	tgtaaagtgt	actagagaaa	acacctatnt	tatgagtcaa	tctagttngt	240
tttattcgac	atgaaggaaa	tttccagatn	acaacactna	caaaactctcc	ctkgackarg	300
ggggacaaa	aaaagcaaaa	ctgamcataa	raaacaatwa	cctggtgaga	arttgcataa	360
acagaaatwr	ggtagtatat	tgaarnacag	catcattaaa	rmgttwkkt	wttctocctt	420
gcaaaaaaca	tgtaacngact	tcccgttgag	taatgccaa	ttgttttttt	tatnataaaa	480
cttgcccttc	attacatggt	tnaaagtgg	gtgggtgggc	aaaatattga	aatgatggaa	540
ctgactgata	aagctgtaca	aataagcagt	gtgcctaaca	agcaacacag	taatgttgac	600
atgcttaatt	cacaaatgct	aatttcatta	taaatgtttg	ctaaaataca	ctttgaacta	660
ttttctgtgn	ttcccagagc	tgagatntta	gattttatgt	agtatnaagt	gaaaaantac	720
gaaataata	acattgaaga	aaaananaaa	aaanaaaaaa	a		761

&lt;210&gt; 189

&lt;211&gt; 482

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(482)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 189

tttttttttt	tttgccgatn	ctactatttt	attgcaggan	gtgggggtgt	atgcaccgca	60
caccggggct	atnagaagca	agaaggaagg	agggagggca	cagccccttg	ctgagcaaca	120
aagccgctg	ctgccttctc	tgtctgtctc	ctgggtcagg	cacatgggga	gaccttcccc	180
aaggcagggg	ccaccagtcc	aggggtggga	atacaggggg	tgggangtgt	gcataagaag	240
tgataggcac	agggcaccgg	gtacagaccc	ctcgggtcct	gacaggtnga	tttcgaccag	300
gtcattgtgc	cctgcccagg	cacagcgtan	atctggaaaa	gacagaatgc	tttccttttc	360
aaatttggt	ngtcatngaa	ngggcanttt	tcctaatng	gctnggtctt	ggtacncttg	420
gttcggccca	gtccncgtc	caaaaantat	tcaccnct	ccnaattgct	tgcnngnccc	480
cc						482

&lt;210&gt; 190

&lt;211&gt; 471

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(471)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 190

tttttttttt	ttttaaaaca	gtttttcaca	acaaaattta	ttagaagaat	agtggttttg	60
aaaactctcg	catccagtga	gaactaccat	acaccacatt	acagctngga	atgtntctcca	120
aatgtctggt	caaatgatac	aatggaacca	ttcaatctta	cacatgcacg	aaagaacaag	180
cgcttttgac	atacaatgca	caaaaaaaaa	aggggggggg	gaccacatgg	attaaaattt	240
taagtactca	tcacatacat	taagacacag	ttctagtcca	gtcnaaaatc	agaactgcnt	300
tgaaaaattt	catgtatgca	atccaaccaa	agaacttnat	tggtgatcat	gantnctcta	360
ctacatcnac	cttgcatt	gccaggaacn	aaaagttnaa	ancacncngt	acaaaaanaa	420
tctgtaattn	anttcaacct	ccgtacngaa	aaatnttnt	tatacactcc	c	471

&lt;210&gt; 191

&lt;211&gt; 402

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(402)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 191

gagggattga	aggtctgttc	tastgtcggm	ctgttcagcc	accaactcta	acaagttgct	60
gtcttccact	cactgtctgt	aagcttttta	acccagacwg	tatcttcata	aatagaacaa	120
attcttacc	agtcacatct	tctaggacct	ttttggattc	agttagtata	agctcttcca	180
cttcctttgt	taagacttca	tctggtaaag	tcttaagttt	tgtagaaagg	aattyaattg	240
ctcgttctct	aacaatgtcc	tctccttgaa	gtatttggt	gaacaacca	cctaaagtcc	300
ctttgtgcat	ccattttaaa	tatacttaat	agggcattgk	tnactaggt	taaattctgc	360
aagagtcatc	tgtctgcaaa	agttgcgtta	gtatatctgc	ca		402



<210> 192  
 <211> 601  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(601)  
 <223> n = A,T,C or G

<400> 192  
 gagctcggat ccaataatct ttgtctgagg gcagcacaca tatncagtgc catggnaact 60  
 ggtctacccc acatgggagc agcatgccgt agntatataa ggtcattccc tgagtcagac 120  
 atgcytyttt gaytaccgtg tgccaagtgc tggtgattct yaacacacyt ccatcccgt 180  
 cttttgtgga aaaactggca cttktctgga actagcarga catcacttac aaattcacc 240  
 acgagacact tgaaggtgt aacaaagcga ytccttgcat gctttttgtc cctccggcac 300  
 cagttgtcaa tactaaccg ctggtttgcc tccatcacat ttgtgatctg tagctctgga 360  
 tacatctcct gacagtactg aagaacttct tcttttgttt caaaagcarg tcttggtgcc 420  
 tgttgatca ggttcccat tcccagtcyg aatgttcaca tggcatattt wacttcccac 480  
 aaaacattgc gatttgaggc tcagcaacag caaatcctgt tccggcattg gctgcaagag 540  
 cctcgatgta gccggccagc gccaaaggcag gcgccgtgag cccaccagc agcagaagca 600  
 g 601

<210> 193  
 <211> 608  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(608)  
 <223> n = A,T,C or G

<400> 193  
 atacagccca natcccacca cgaagatgcg cttgttgact gagaacctga tgcggctcact 60  
 ggtcccgtg tagccccagc gactctccac ctgctggaag cggttgatgc tgcaactcyt 120  
 cccaacgcag gcagmagcgg gscgggtcaa tgaactccay tcgtggcttg gggtkgacgg 180  
 tkaagtgcag gaagaggtg accacctcgc ggtccaccag gatgcccgac tgtgcgggac 240  
 ctgcagcgaa actcctcgat ggtcatgagc ggaagcgaa tgaggcccag ggccttgccc 300  
 agaaccttc gctgttctc tggcgtcacc tgcagctgct gccgtgaca ctgggcctcg 360  
 gaccagcgga caaacggcrt tgaacagccg cacctcacgg atgccagtg tgtcgcgctc 420  
 caggammgsc accagcgtgt ccaggtcaat gtcggtgaag ccctccgcgg gtrattggcg 480  
 ctgcagtgtt tttgtcgatg ttctccaggc acaggctggc cagctgcggt tcatcgaaga 540  
 gtcgcgcctg cgtgagcagc atgaaggcgt tgtcggtcg cagttcttct tcaggaactc 600  
 cagcgaat 608

<210> 194  
 <211> 392  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(392)  
 <223> n = A,T,C or G

<400> 194  
 gaacggctgg accttgccctc gcattgtgct tgctggcagg gaataccttg gcaagcagyt 60

```

ccagtcgag cagccccaga ccgctgcgc ccgaagctaa gcctgcctct ggccctcccc 120
tccgcctcaa tgcagaacca gtagtgggag cactgtgttt agagttaaga gtgaacactg 180
tttgatttta cttgggaatt tcctctgtta tatagctttt cccaatgcta atttccaaac 240
aacaacaaca aaataacatg tttgcctgtt aagttgtata aaagtaggtg attctgtatt 300
taaagaaaat attactgtta catatactgc ttgcaatttc tgtatttatt gktnctstgg 360
aaataaatat agttattaaa ggtgtcant cc 392

```

```

<210> 195
<211> 502
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(502)
<223> n = A,T,C or G

```

```

<400> 195
ccsttkgagg ggtkaggkyc cagttyccga gtggaagaaa caggccagga gaagtgcgtg 60
ccgagctgag gcagatgttc ccacagtgc cccagagacc stgggstata gtytctgacc 120
cctcncaagg aaagaccacs ttctggggac atgggctgga gggcaggacc tagaggcacc 180
aagggaaggc ccatttccgg ggstgttccc cgaggaggaa gggaaggggc tctgtgtgcc 240
ccccasgagg aagaggccct gagtccctgg atcagacacc ccttcacgtg tatccccaca 300
caaatgcaag ctacaccaagg tcccctctca gtccccttcc stacaccctg amcggccact 360
gscscacacc caccagagc acgccaccg ccatggggar tgtgctcaag gartcgcnng 420
gcarcgtgga catctngtcc cagaaggggg cagaatctcc aatagangga ctgarcmstt 480
gctnanaaaa aaaaanaaaa aa 502

```

```

<210> 196
<211> 665
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(665)
<223> n = A,T,C or G

```

```

<400> 196
ggttacttg tttcattgcc accacttagt ggatgtcatt tagaaccatt ttgtctgctc 60
cctctggaag ccttgccgag agcggacttt gtaattgttg gagaataact gctgaatttt 120
wagctgtttk gatttgatts gcaccactgc acccacaact tcaatatgaa aacyawttga 180
actwatthtat tatcttgta aaagtataac aatgaaaatt ttgttcatac tgtattkac 240
aagtatgatg aaaagcaawa gatatatatt cttttattat gttaaattat gattgccatt 300
attaatcggc aaaatgtgga gtgtatgttc ttttcacagt aatatatgcc ttttgtaact 360
tcacttggtt attttattgt aaatgartta caaaattcct aatttaagar aatggtatgt 420
watatttatt tcattaattt ctttcctkgt ttacgtwaat ttgaaaaga wtgcatgatt 480
tcttgacaga aatcgatcct gatgctgtgg aagtagtttg acccacatcc ctatgagttt 540
ttcttagaat gtataaagggt ttagagccat cnaacttcaa agaaaaaat gaccacatac 600
tttgaatca ggctgaaatg tggcatgctn ttctaattcc aactttataa actagcaaan 660
aagtg 665

```

```

<210> 197
<211> 492
<212> DNA
<213> Homo sapien

```

```

<220>

```

<221> misc\_feature  
 <222> (1)...(492)  
 <223> n = A,T,C or G

<400> 197  
 tttntttttt ttttttttgc aggaaggatt ccattttattg tggatgcatt ttcacaatat 60  
 atgtttattg gagcgatcca ttatcagtga aaagtatcaa gtgtttataa natttttagg 120  
 aaggcagatt cacagaacat gctngtcngc ttgcagtttt acctcgtana gatnacagag 180  
 aattatagtc naaccagtaa acnaggaatt tacttttcaa aagattaaat ccaaactgaa 240  
 caaaattcta ccctgaaact tactccatcc aaatattgga ataanagtca gcagtgtac 300  
 attctcttct gaactttaga ttttctagaa aaatatgtaa tagtgatcag gaagagctct 360  
 tgttcaaaag tacaacnaag caatgttccc ttacatagg ccttaattca aactttgatc 420  
 catttctctc ccacacggg agtcaatgct acctgggaca cttgtatttt gttcatnctg 480  
 aancgtgctt aa 492

<210> 198  
 <211> 478  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(478)  
 <223> n = A,T,C or G

<400> 198  
 tttnttttgn atttcantct gtannaanta ttttcattat gtttattana aaaatatnaa 60  
 tgtntccacn acaaatcatn ttacntnagt aagaggccan ctacattgta caacatacac 120  
 tgagtatttt ttgaaaagga caagttttaa gtanacncat attgccganc atancacatt 180  
 tatacatggc ttgattgata tttagcacag canaaactga gtgagttacc agaaanaaat 240  
 natatatgtc aatcngattt aagatacaaa acagatccta tgggtacatan catcntgtag 300  
 gagttgtggc tttatgttta ctgaaagtca atgcagttcc tgtacaaaga gatggccgta 360  
 agcattctag tacctctact ccattgttaa gaatcgtaca cttatgttta catatgtnta 420  
 gggtaagaat tgtgttaaagt naanttatgg agaggtccan gagaaaaatt tnatncaa 478

<210> 199  
 <211> 482  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(482)  
 <223> n = A,T,C or G

<400> 199  
 agtgacttgt cctccaacaa aacccttga tcaagtttgt ggcaactgaca atcagacctta 60  
 tgctagttcc tgtcatctat tcgctactaa atgcagactg gaggggacca aaaaggggca 120  
 tcaactccag ctggattatt ttggagcctg caaatctatt cctacttgta cggactttga 180  
 agtgattcag tttcctctac ggatgagaga ctggctcaag aatatcctca tgcagcttta 240  
 tgaagccnac tctgaacacg ctggttatct nagatgagaa ncagagaaat aaagtcnaga 300  
 aaatttacct ggangaaaag aggccttngg ctggggacca tccattgaa ccttctctta 360  
 anggacttta agaanaaaact accacatgtn tgtngtatcc tgggtgccngg ccgtttantg 420  
 aacntngacn ncacccttnt ggaatanant cttgacngcn tcctgaactt gtcctctgc 480  
 ga 482

<210> 200  
 <211> 270

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(270)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 200

cggccgcaag	tgcaactcca	gctggggccg	tgccggacgaa	gattctgcca	gcagttggtc	60
cgactgcgac	gacggcggcg	gcgacagtcg	caggtgcagc	gcgggcgcct	ggggtcttgc	120
aaggctgagc	tgacgccgca	gaggtcgtgt	cacgtcccac	gaccttgacg	ccgtcgggga	180
cagccggaac	agagcccggt	gaangcggga	ggcctcgggg	agcccctcgg	gaagggcggc	240
ccgagagata	cgcaggtgca	ggtggccgcc				270

&lt;210&gt; 201

&lt;211&gt; 419

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(419)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 201

tttttttttt	ttttggaatc	tactgcgagc	acagcaggtc	agcaacaagt	ttattttgca	60
gctagcaagg	taacagggtg	gggcatggtt	acatgttcag	gtcaacttcc	tttgtcgtgg	120
ttgattggtt	tgtctttatg	ggggcggggg	ggggtagggg	aaancgaagc	anaantaaca	180
tgagtggtt	gcaccctccc	tgtagaacct	ggttacnaaa	gcttggggca	gttcacctgg	240
tctgtgacgg	tcatTTTTctt	gacatcaatg	ttattagaag	tcaggatatc	tttagagag	300
tccactgtnt	ctggaggagg	attagggttt	cttgccaana	tccaancaaa	atccacntga	360
aaaagttgga	tgatncangt	acngaatacc	ganggcatan	tttctatant	cggtaggcca	419

&lt;210&gt; 202

&lt;211&gt; 509

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(509)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 202

tttntttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	tttttttttt	60
tggcacttaa	tccattttta	tttcaaaatg	tctacaaant	ttnaatncnc	cattatacng	120
gtnattttnc	aaaatctaaa	nnttattcaa	attnagacca	aantccttac	ncaaatnnaa	180
tacnncnaaa	aatcaaaaaat	atacntntct	ttcagcaaac	ttngttacat	aaattaaaaa	240
aatatatacg	gctgggtgtt	tcaaagtaca	attatcttaa	cactgcaaac	atnttttnnaa	300
ggaactaaaa	taaaaaaaa	cactnccgca	aagggttaaag	ggaacaacaa	attcntttta	360
caacancnnc	nattataaaa	atcatatctc	aaatcttagg	ggaatatata	cttcacacng	420
ggatcttaac	ttttactnca	ctttgtttat	ttttttanaa	ccattgtntt	gggcccaaca	480
caatggnaat	ncnccnncnc	tgactagt				509

&lt;210&gt; 203

&lt;211&gt; 583

&lt;212&gt; DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(583)

<223> n = A,T,C or G

<400> 203

tttttttttt	ttttttttga	ccccctctt	ataaaaaaca	agttaccatt	ttattttact	60
tacacatatt	tattttataa	ttggtattag	atattcaaaa	ggcagctttt	aaaatcaaac	120
taaatggaaa	ctgccttaga	tacataattc	ttaggaatta	gcttaaaatc	tgccataaagt	180
gaaaatcttc	tctagctctt	ttgactgtaa	atttttgact	cttgtaaaac	atccaaattc	240
atttttcttg	tctttaaaaa	tatctaattc	ttccattttt	tccctattcc	aagtcaattt	300
gcttctctag	cctcatttcc	tagctcttat	ctactattag	taagtggctt	ttttcctaaa	360
agggaaaaca	ggaagagana	atggcacaca	aaacaaacat	tttatattca	tatttctacc	420
tacgttaata	aaatagcatt	ttgtgaagcc	agctcaaaag	aaggcttaga	tccttttatg	480
tccatttttag	tcactaaacg	atatcnaaag	tgccagaatg	caaaagggtt	gtgaacattt	540
attcaaaagc	taatataaga	tatttcacat	actcatcttt	ctg		583

<210> 204

<211> 589

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(589)

<223> n = A,T,C or G

<400> 204

ttttttttnt	tttttttttt	tttttttctc	ttcttttttt	ttganaatga	ggatcgagtt	60
tttactctc	tagatagggc	atgaagaaaa	ctcatctttc	cagctttaaa	ataacaatca	120
aatctcttat	gctatatcat	attttaagtt	aaactaatga	gtcactggct	tatcttctcc	180
tgaaggaaat	ctgttcattc	ttctcattca	tatagttata	tcaagtacta	ccttgcatat	240
tgagagggtt	ttcttctcta	tttacacata	tatttccatg	tgaatttgta	tcaaaccttt	300
attttcatgc	aaactagaaa	ataatgtntt	cttttgcata	agagaagaga	acaatatnag	360
cattacaaaa	ctgctcaaat	tgtttgtaa	gnttatccat	tataattagt	tnggcaggag	420
ctaatacaaa	tcacatttac	ngacnagcaa	taataaaact	gaagtaccag	ttaaatatcc	480
aaaaataatta	aaggaacatt	tttagcctgg	gtataattag	ctaattcact	ttacaagcat	540
ttattnagaa	tgaattcaca	tgttattatt	cntagccca	acacaatgg		589

<210> 205

<211> 545

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(545)

<223> n = A,T,C or G

<400> 205

ttttnttttt	ttttttcagt	aataatcaga	acaatattta	tttttatatt	taaaattcat	60
agaaaagtgc	cttacattta	ataaaaagttt	gtttctcaaa	gtgatcagag	gaattagata	120
tngtcttgaa	caccaatatt	aatttgagga	aaatacacca	aaatacatta	agtaaattat	180
ttaagatcat	agagcttgta	agtgaagaga	taaaatttga	cctcagaaac	tctgagcatt	240
aaaaatccac	tattagcaaa	taaattacta	tggaacttct	gctttaattt	tgtgatgaat	300
atgggggtgc	actggtaaac	caacacattc	tgaaggatac	attacttagt	gatagattct	360

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tatgtacttt gctanatnac gtggatatga gttgacaagt ttctctttct tcaatctttt 420
aaggggcnga ngaaatgagg aagaaaagaa aaggattacg catactgttc tttctatngg 480
aaggattaga tatgtttcct ttgccaatat taaaaaata ataatgttta ctactagtga 540
aacc 545

```

```

<210> 206
<211> 487
<212> DNA
<213> Homo sapien

```

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<220>
<221> misc_feature
<222> (1)...(487)
<223> n = A,T,C or G

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```

<400> 206
tttttttttt ttttttagtc aagtttctna tttttattat aattaaagtc ttggtcattt 60
catttattag ctctgcaact tacatattta aattaaagaa acgttnttag acaactgtna 120
caatttataa atgtaagggtg ccattattga gtanatatat tcctccaaga gtggatgtgt 180
cccttctccc accaactaat gaancagcaa cattagtta attttattag tagatnatac 240
actgctgcaa acgctaattc tcttctccat ccccatgtng atattgtgta tatgtgtgag 300
ttggttagaa tgcatacanca atctnacaat caacagcaag atgaagctag gcntgggctt 360
tcggtgaaaa tagactgtgt ctgtctgaat caaatgatct gacctatcct cggtggaag 420
aactcttga accgcttcct caaaggcngc tgccacattt gtggcntctn ttgcacttgt 480
ttcaaaa 487

```

```

<210> 207
<211> 332
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(332)
<223> n = A,T,C or G

```

```

<400> 207
tgaattggct aaaagactgc atttttanaa ctagcaactc ttatttcttt cctttaaaaa 60
tacatagcat taaatcccaa atcctattta aagacctgac agcttgagaa ggtcactact 120
gcatttatag gaccttctgg tggttctgct gttacntttg aantctgaca atccttgana 180
atctttgcat gcagaggagg taaaagggtat tggattttca cagaggaana acacagcgca 240
gaaatgaagg ggccaggctt actgagcttg tccactggag ggctcatggg tgggacatgg 300
aaaagaaggc agcctaggcc ctggggagcc ca 332

```

```

<210> 208
<211> 524
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(524)
<223> n = A,T,C or G

```

```

<400> 208
aggcggtggg gcggaggggc ttactgtttt gtctcagtaa caataaatac aaaaagactg 60
gttggtttcc ggccccatcc aaccacgaag ttgatttctc ttgtgtgcag agtgactgat 120
tttaaaggac atggagcttg tcacaatgtc acaatgtcac agtgtgaagg gcacactcac 180

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tcccgcgtga ttcacattta gcaaccaaca atagctcatg agtcataact tgtaaataact	240
tttggcagaa tacttnttga aacttgcaga tgataactaa gatccaagat atttcccaaa	300
gtaaatagaa gtgggtcata atattaatta cctgttcaca tcagcttcca tttacaagtc	360
atgagcccag acactgacat caaactaagc ccacttagac tcctcaccac cagtctgtcc	420
tgatcatcaga caggaggctg tcaccttgac caaattctca ccagtcaatc atctatccaa	480
aaaccattac ctgatccact tccggtaatg caccaccttg gtga	524

<210> 209  
 <211> 159  
 <212> DNA  
 <213> Homo sapien

<400> 209	
gggtgaggaa atccagagtt gccatggaga aaattccagt gtcagcattc ttgctccttg	60
tggccctctc ctacactctg gccagagata ccacagtcaa acctggagcc aaaaaggaca	120
caaaggactc tcgacccaaa ctgccccaga ccctctcca	159

<210> 210  
 <211> 256  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(256)  
 <223> n = A,T,C or G

<400> 210	
actccctggc agacaaggc agaggagaga gctctgttag ttctgtgttg ttgaactgcc	60
actgaatttc tttccacttg gactattaca tgccanttga gggactaatg gaaaaacgta	120
tggggagatt ttanccaatt tangtntgta aatggggaga ctggggcagg cgggagagat	180
ttgcaggggtg naaatgggan ggctggtttg ttanatgaac agggacatag gaggtaggca	240
ccaggatgct aaatca	256

<210> 211  
 <211> 264  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(264)  
 <223> n = A,T,C or G

<400> 211	
acattgtttt tttagataa agcattgaga gagctctcct taacgtgaca caatggaagg	60
actggaacac ataccacat ctttgttctg agggataatt ttctgataaa gtcttgctgt	120
atattcaagc acatattgta tatattattc agttccatgt ttatagccta gttaaggaga	180
ggggagatac attcngaaag aggactgaaa gaaatactca agtnggaaaa cagaaaaaga	240
aaaaaggag caaatgagaa gcct	264

<210> 212  
 <211> 328  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature

&lt;222&gt; (1)...(328)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 212

acccaaaaat ccaatgctga atatttggct tcattattcc canattcttt gattgtcaaa	60
ggattttaatg ttgtctcagc ttgggcactt cagttaggac ctaaggatgc cagccggcag	120
gtttatatat gcagcaacaa tattcaagcg cgacaacagg ttattgaact tgcccggcag	180
ttnaatttca ttccattga cttgggatcc ttatcatcag ccagagagat tgaaaattta	240
cccctacnac tctttactct ctgganaggg ccagtgtgtg tagctataag cttggccaca	300
tttttttttc ctttattcct ttgtcaga	328

&lt;210&gt; 213

&lt;211&gt; 250

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(250)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 213

acttatgagc agagcgacat atccnagtgt agactgaata aaactgaatt ctctccagtt	60
taaagcattg ctactgaag ggatagaagt gactgccagg agggaaagta agccaaggct	120
cattatgcc aagganatat acatttcaat tctccaaact tcttcctcat tccaagagtt	180
ttcaatattt gcatgaacct gctgataanc catgttaana aacaaatata tctctnacct	240
tctcatcggt	250

&lt;210&gt; 214

&lt;211&gt; 444

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(444)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 214

accagaatc caatgctgaa tatttggctt cattattccc agattctttg attgtcaaag	60
gattttaatgt tgtctcagct tgggcacttc agttaggacc taaggatgcc agccggcagg	120
tttatatatg cagcaacaat attcaagcgc gacaacaggt tattgaactt gcccgccagt	180
tgaatttcat tccattgac ttgggatcct tatcatcagc canagagatt gaaaatttac	240
ccctacgact ctttactctc tggagagggc cagtgtgtgt agctataagc ttggccacat	300
ttttttttcc tttattcctt tgtcagagat gcgattcatc catatgctan aaaccaacag	360
agtgactttt acaaaattcc tataganatt gtgaataaaa ccttacctat agttgccatt	420
actttgctct ccctaataata cctc	444

&lt;210&gt; 215

&lt;211&gt; 366

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(366)

&lt;223&gt; n = A,T,C or G



<400> 215  
 acttatgagc agagcgacat atccaagtgt anactgaata aaactgaatt ctctccagtt 60  
 taaagcattg ctactgaag ggatagaagt gactgccagg agggaaagta agccaaggct 120  
 cattatgcca aagganatat acatttcaat tctccaaact tcttcctcat tccaagagtt 180  
 ttcaatattt gcatgaacct gctgataagc catgttgaga aacaaatata tctctgacct 240  
 tctcatcggt aagcagaggc tgtaggcaac atggaccata gcgaanaaaa aacttagtaa 300  
 tccaagctgt tttctacact gtaaccagggt ttccaaccaa ggtggaaatc tcctatactt 360  
 ggtgcc 366

<210> 216  
 <211> 260  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(260)  
 <223> n = A,T,C or G

<400> 216  
 ctgtataaac agaactccac tgcangaggg agggccgggc caggagaatc tccgcttgtc 60  
 caagacaggg gcctaaggag ggtctccaca ctgctnntaa gggctnttnc atttttttat 120  
 taataaaaag tnnaaaaggc ctcttctcaa cttttttccc ttnggctgga aaatttaaaa 180  
 atcaaaaatt tcctnaagtt ntcaagctat catatatact ntatcctgaa aaagcaacat 240  
 aattcttctt tcctccttt 260

<210> 217  
 <211> 262  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(262)  
 <223> n = A,T,C or G

<400> 217  
 acctacgtgg gtaagtttan aaatgttata atttcaggaa naggaacgca tataattgta 60  
 tcttgccat aattttctat ttaataagg aaatagcaaa ttgggggtggg gggaatgtag 120  
 ggcattctac agtttgagca aaatgcaatt aaatgtggaa ggacagcact gaaaaatttt 180  
 atgaataatc tgatgatta tatgtctcta gagtagattt ataattagcc acttacccta 240  
 atatccttca tgcttgtaaa gt 262

<210> 218  
 <211> 205  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(205)  
 <223> n = A,T,C or G

<400> 218  
 accaaggtgg tgcattaccg gaantggatc aangacacca tctgtggcaa cccctgagca 60  
 cccctatcaa ctcccttttg tagtaaaactt ggaaccttg aaatgaccag gccaaagactc 120  
 aggctcccc agttctactg acctttgtcc ttangntna ngtccagggt tgctaggaaa 180  
 anaaatcagc agacacagggt gtaaa 205

<210> 219  
 <211> 114  
 <212> DNA  
 <213> Homo sapien

<400> 219  
 tactgttttg tctcagtaac aataaatata aaaagactgg ttgtgttccg gcccaccca 60  
 accacgaagt tgatttctct tgtgtgcaga gtgactgatt ttaaaggaca tgga 114

<210> 220  
 <211> 93  
 <212> DNA  
 <213> Homo sapien

<400> 220  
 actagccagc acaaaaaggca gggtagcctg aattgctttc tgctctttac atttctttta 60  
 aaataagcat ttagtgctca gtcctactg agt 93

<210> 221  
 <211> 167  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(167)  
 <223> n = A,T,C or G

<400> 221  
 actangtgca ggtgcgcaca aatatttgct gatattccct tcatottgga ttccatgagg 60  
 tcttttgccc agcctgtggc tctactgtag taagtttctg ctgatgagga gccagnatgc 120  
 cccccactac cttccctgac gtcccccana aatcacccaa cctctgt 167

<210> 222  
 <211> 351  
 <212> DNA  
 <213> Homo sapien

<400> 222  
 agggcggtgt ggcggaggcg gtactgacct cattagtagg aggatgcatt ctggcacccc 60  
 gttcttcacc tgtcccccaa tccttaaaag gccatactgc ataaagtcaa caacagataa 120  
 atgtttgctg aattaaagga tggatgaaaa aaattaataa tgaatttttg cataatccaa 180  
 ttttctcttt tatatttcta gaagaagttt ctttgagcct attagatccc gggaatcttt 240  
 taggtgagca tgattagaga gctttagagt tgcttttaca tatatctggc atatttgagt 300  
 ctcgtatcaa aacaatagat tggtaaagggt ggtattattg tattgataag t 351

<210> 223  
 <211> 383  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(383)  
 <223> n = A,T,C or G

<400> 223

aaaacaaaca aacaaaaaaa acaattcttc attcagaaaa attatcttag ggactgatat	60
tggtaatat ggtcaattta atwrtttkt ggggcatttc cttacattgt cttgacaaga	120
ttaaaaatgtc tgtgccaaaa ttttgtattt tatttggaga cttcttatca aaagtaatgc	180
tgccaaagga agtctaagga attagtagtg ttcccmtcac ttgtttggag tgtgctattc	240
taaaagattt tgatttcctg gaatgacaat tataatttaa ctttgggtggg ggaaanagtt	300
ataggaccac agtcttcact tctgatactt gtaaattaat cttttattgc acttgttttg	360
accattaagc tatatgttta aaa	383

&lt;210&gt; 224

&lt;211&gt; 320

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 224

cccctgaagg cttcttggtta gaaaatagta cagttacaac caataggaac aacaaaaaga	60
aaaagtittgt gacattgtag tagggagtgt gtaccctta ctcccatca aaaaaaaaat	120
ggatacatgg ttaaaggata raagggaat attttatcat atgttctaaa agagaaggaa	180
gagaaaatac tactttctcr aaatggaagc ccttaaaggt gctttgatac tgaaggacac	240
aaatgtggcc gtccatcctc ctttaragtt gcatgacttg gacacggtaa ctgttgcaat	300
tttaractcm gcattgtgac	320

&lt;210&gt; 225

&lt;211&gt; 1214

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 225

gaggactgca gcccgcactc gcagccctgg caggcggcac tggatcatgga aaacgaattg	60
ttctgctcgg gcgtcctggt gcatccgcag tgggtgctgt cagccgcaca ctgtttccag	120
aactcctaca ccatcgggct gggcctgcac agtcttgagg ccgaccaaga gccaggagc	180
cagatgggtg aggccagcct ctccgtacgg caccagagt acaacagacc cttgctcgt	240
aacgacctca tgcctcatca gttggacgaa tccgtgtccg agtctgacac catccggagc	300
atcagcattg cttcgcagtg ccctaccgag gggaaactct gcctcgtttc tggctgggg	360
ctgctggcga acggcagaat gcctaccgtg ctgcagtgcg tgaaacgtgtc ggtggtgtct	420
gaggaggtct gcagtaagct ctatgaccgg ctgtaccacc ccagcatgtt ctgcgcgggc	480
ggagggaag accagaagga ctctgcaac ggtgactctg gggggcccct gatctgcaac	540
gggtacttgc agggccttgt gtctttcgga aaagcccgt gtggccaagt tggcgtgcca	600
ggtgtctaca ccaacctctg caaattcact gagggtatag agaaaaccgt ccaggccagt	660
taactctggg gactgggaac ccatgaaatt gacccccaaa tcatcctgc ggaaggaatt	720
caggaatata tgttcccagc ccctcctccc tcaggcccag gaggccagg cccagcccc	780
tcctccctca aaccaagggt acagatcccc agcccctcct ccctcagacc caggagtcca	840
gacccccag cccctcctcc ctgagaccga ggagtccagc ccctcctccc tcagaccag	900
gagtccagac cccccagccc ctctccctc agaccagggt gtccaggccc ccaaccctc	960
ctccctcaga ctgagaggtc caagccccc acccctcctt cccagaccct agaggtccag	1020
gtcccagccc ctctcctc agaccagcg gtccaatgcc acctagactc tccctgtaca	1080
cagtcccc ttgtggcagc ttgacccaac cttaccagtt gggttttcat tttttgtccc	1140
tttcccttag atccagaaat aaagtctaag agaagcgcaa aaaaaaaaaa aaaaaaaaaa	1200
aaaaaaaaaa aaaa	1214

&lt;210&gt; 226

&lt;211&gt; 119

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 226

accagtatg tgcagggaga cggaacccca tgtgacagcc cactccacca gggttcccaa	60
agaacctggc ccagtcataa tcattcatcc tgacagtggc aataatcacg ataaccagt	119

<210> 227  
 <211> 818  
 <212> DNA  
 <213> Homo sapien

<400> 227  
 acaattcata gggacgacca atgaggacag ggaatgaacc cggctctccc ccagccctga 60  
 tttttgctac atatggggtc ctttttcatt ctttgcaaaa aacttggtt ttctgagaac 120  
 acggacggtt cttagcaciaa tttgtgaaat ctgtgtaraa ccgggctttg caggggagat 180  
 aattttcctc ctctggagga aaggtggtga ttgacaggca gggagacagt gacaaggcta 240  
 gagaaagcca cgctcggcct tctctgaaac aggatggaac ggcagacccc tgaaaacgaa 300  
 gcttgtcccc ttccaatcag ccaacttctga gaacccccat ctaacttcct actggaaaag 360  
 agggcctcct caggagcagt ccaagagttt tcaaagataa cgtgacaact accatctaga 420  
 ggaaagggtg caccctcagc agagaagccg agagcttaac tctggtcgtt tccagagaca 480  
 acctgctggc tgtcttggga tgcgccagc ctttgagagg ccactacccc atgaacttct 540  
 gccatccact ggacatgaag ctgaggacac tgggcttcaa cactgagttg tcatgagagg 600  
 gacaggctct gccctcaagc cggctgaggg cagcaaccac tctcctccc tttctcacgc 660  
 aaagccattc ccacaaatcc agaccatacc atgaagcaac gagacccaaa cagtttggct 720  
 caagaggata tgaggactgt ctacgcctgg ctttgggctg acaccatgca cacacacaag 780  
 gtccacttct aggttttcag cctagatggg agtcgtgt 818

<210> 228  
 <211> 744  
 <212> DNA  
 <213> Homo sapien

<400> 228  
 actggagaca ctgttgaact tgatcaagac ccagaccacc ccaggtctcc ttcgtgggat 60  
 gtcatacgt ttgacatacc tttggaacga gcctcctcct tggaaatgg aagaccgtgt 120  
 tcgtggccga cctggcctct cctggcctgt ttcttaagat gcggagtcac atttcaatgg 180  
 taggaaaagt ggcttcgtaa aatagaagag cagtcactgt ggaactacca aatggcgaga 240  
 tgctcgggtc acattggggg gctttgggat aaaagattta tgagccaact attctctggc 300  
 accagattct aggcagttt gttccactga agcttttccc acagcagtc acctctgcag 360  
 gctggcagct gaatggcttg ccggtggctc tgtggcaaga tcacactgag atcgatgggt 420  
 gagaaggcta ggatgcttgt ctagtgttct tagctgtcac gttggctcct tccaggttgg 480  
 ccagacggtg ttggccactc ctttctaaaa cacaggcgcc ctccgtgtga cagtgaaccg 540  
 ccgtggtatg ccttggccca ttccagcagt ccagttatg catttcaagt ttggggtttg 600  
 ttcttttcgt taatgttct ctgtgttgc agctgtcttc atttctctgg ctaagcagca 660  
 ttgggagatg tggaccagag atccactcct taagaaccag tggcgaaaga cactttcttt 720  
 cttcactctg aagtagctgg tggg 744

<210> 229  
 <211> 300  
 <212> DNA  
 <213> Homo sapien

<400> 229  
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 cattacacat cgaaataaaa gaaaggtggc agacttgccc aacgccaggc tgacatgtgc 120  
 tgcagggttg ttgtttttta attattattg ttgaaacgt caccacagt ccctgttaat 180  
 ttgtatgtga cagccaactc tgagaaggtc ctatttttcc acctgcagag gatccagctc 240  
 cactaggctc ctccctgccc tcacactgga gtctccgcca gtgtgggtgc ccactgacat 300

<210> 230  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

&lt;400&gt; 230

cagcagaaca	aatacaata	tgaagagtgc	aaagatctca	taaaatctat	gctgaggaat	60
gagcgacagt	tcaaggagga	gaagcttgca	gagcagctca	agcaagctga	ggagctcagg	120
caatataaag	tcctgggtca	cactcaggaa	cgagagctga	cccagttaag	ggagaagttg	180
cggaagggga	gagatgcctc	cctctcattg	aatgagcatc	tccaggccct	cctcactccg	240
gatgaaccgg	acaagtccca	ggggcaggac	ctccaagaaa	cagacctcgg	ccgcgaccac	300
g						301

&lt;210&gt; 231

&lt;211&gt; 301

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 231

gcaagcacgc	tggcaaatct	ctgtcaggtc	agctccagag	aagccattag	tcatttttagc	60
caggaactcc	aagtccacat	ccttggaac	tggggacttg	cgcaggttag	ccttgaggat	120
ggcaacacgg	gacttctcat	caggaagtgg	gatgtagatg	agctgatcaa	gacggccagg	180
tctgaggatg	gcaggatcaa	tgatgtcagg	ccggttggtg	ccgccaatga	tgaacacatt	240
ttttttgtg	gacatgccat	ccatttctgt	caggatctgg	ttgatgactc	ggtcagcagc	300
c						301

&lt;210&gt; 232

&lt;211&gt; 301

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 232

agtaggtatt	tcgtgagaag	ttcaacacca	aaactggaac	atagttctcc	ttcaagtgtt	60
ggcgacagcg	gggcttcctg	attctggaat	ataactttgt	gtaaattaac	agccacctat	120
agaagagtcc	atctgctgtg	aaggagagac	agagaactct	gggttcctgc	gtcctgtcca	180
cgtgctgtac	caagtgtctg	tgccagcctg	ttacctgttc	tactgaaaa	tctggctaat	240
gctcttgtgt	atcacttctg	attctgacaa	tcaatcaatc	aatggcctag	agcactgact	300
g						301

&lt;210&gt; 233

&lt;211&gt; 301

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 233

atgactgact	tcccagtaag	gctctctaag	gggtaagtag	gaggatccac	aggatttgag	60
atgctaaggc	cccagagatc	gtttgatcca	accctcttat	tttcagaggg	gaaaatgggg	120
cctagaagtt	acagagcatc	tagctggtgc	gctggcacc	ctggcctcac	acagactccc	180
gagtagctgg	gactacaggc	acacagtcac	tgaagcaggc	cctgttagca	attctatgcg	240
tacaaattaa	catgagatga	gtagagactt	tattgagaaa	gcaagagaaa	atcctatcaa	300
c						301

&lt;210&gt; 234

&lt;211&gt; 301

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 234

aggtcctaca	catcgagact	catccatgat	tgatatgaat	ttaaaaatta	caagcaaaga	60
cattttatcc	atcatgatgc	tttcttttgt	ttctcttttt	cgttttcttc	ttttcttttt	120
tcaatttcag	caacatactt	ctcaatttct	tcaggattta	aaatcttgag	ggattgatct	180
cgctcatga	cagcaagttc	aatgtttttg	ccacctgact	gaaccacttc	caggagtgcc	240
ttgatcacca	gcttaatggg	cagatcatct	gcttcaatgg	cttcgtcagt	atagttcttc	300

t

301

<210> 235  
 <211> 283  
 <212> DNA  
 <213> Homo sapien

<400> 235  
 tggggctgtg catcaggcgg gtttgagaaa tattcaattc tcagcagaag ccagaatttg 60  
 aattccctca tcttttaggg aatcatttac caggtttgga gaggattcag acagctcagg 120  
 tgctttcact aatgtctctg aacttctgtc cctctttgtt catggatagt ccaataaata 180  
 atgttatctt tgaactgatg ctcataggag agaataaag aactctgagt gatatcaaca 240  
 ttagggattc aaagaaatat tagatttaag ctcacactgg tca 283

<210> 236  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 236  
 aggtcctcca ccaactgcct gaagcacggg taaaattggg aagaagtata gtgcagcata 60  
 aatactttta aatcgatcag atttccctaa cccacatgca atcttcttca ccagaagagg 120  
 tcggagcagc atcattaata ccaagcagaa tgcgtaatag ataaatacaa tggatatatg 180  
 tgggtagacg gcttcattgag tacagtgtac tgtgggatcg taatctggac ttgggttgta 240  
 aagcatcgtg taccagtcag aaagcatcaa tactcgacat gaacgaatat aaagaacacc 300  
 a 301

<210> 237  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 237  
 cagtggtagt ggtgggtggac gtggcggttg tctggtgtgc ttttttgggtg cccgtcacaa 60  
 actcaatttt tggtcgctcc tttttggcct ttccaattt gtccatctca attttctggg 120  
 ccttggctaa tgccatcatg taggagtcct cagaccagcc atggggatca aacatatcct 180  
 ttgggtagtt ggtgccaagc tegtcaatgg cacagaatgg atcagcttct cgtaaatcta 240  
 gggttccgaa attctttctt cctttggata atgtagttca tatccattcc ctcccttata 300  
 t 301

<210> 238  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 238  
 gggcagggtt tttttttttt ttttttgatg gtgcagaccc ttgctttatt tgtctgactt 60  
 gttcacagtt cagccccctg ctcaaaaaac caacgggcca gctaaggaga ggaggaggca 120  
 ccttgagact tccggagtcg aggtctctca gggttcccca gcccatcaat cattttctgc 180  
 accccctgcc tgggaagcag ctccctgggg ggtgggaatg ggtgactaga agggatttca 240  
 gtgtgggacc cagggctctg tcttcacagt aggaggtgga agggatgact aatttcttta 300  
 t 301

<210> 239  
 <211> 239  
 <212> DNA  
 <213> Homo sapien

<400> 239  
 ataagcagct aggggaattct ttatttagta atgtcctaac ataaaagttc acataactgc 60  
 ttctgtcaaa ccatgatact gagctttgtg acaaccaga aataactaag agaaggcaaa 120  
 cataatacct tagagatcaa gaaacattta cacagttaa ctgtttaaaa atagctcaac 180  
 attcagccag tgagtagagt gtgaatgcc aacatacacg tatacaggtc cttcaggga 239

<210> 240  
 <211> 300  
 <212> DNA  
 <213> Homo sapien

<400> 240  
 ggtcctaag aagcagcagc ttccacattt taacgcaggt ttacggtgat actgtccttt 60  
 gggatctgcc ctccagtggg accttttaag gaagaagtgg gccaagcta agttccacat 120  
 gctgggtgag ccagatgact tctgttcctt ggtcactttc ttcaatgggg cgaatggggg 180  
 ctgccagggt tttaaaatca tgcttcatct tgaagcacac ggtcacttca ccctctcac 240  
 gctgtgggtg tactttgatg aaaataccca ctttgttggc ctttctgaag ctataatgtc 300

<210> 241  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 241  
 gaggtctggt gctgaggtct ctgggctagg aagaggaggt ctgtggagct ggaagccaga 60  
 cctctttgga ggaaactcca gcagctatgt tgggtgtctct gagggaatgc aacaaggctg 120  
 ctctccatg tattggaaaa ctgcaactg gactcaactg gaagggaagt ctgctgccag 180  
 tgtgaagaac cagcctgagg tgacagaaac ggaagcaaac aggaacagcc agtcttttct 240  
 tcctcctcct gtcatacggg ctctctcaag catcctttgt tgtcaggggc ctaaaaggga 300  
 g 301

<210> 242  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 242  
 ccgaggtoct gggatgcaac caatcactct gtttcacgtg acttttatca ccatacaatt 60  
 tgtggcattt cctcattttc tacattgtag aatcaagagt gtaaataaat gtatatcgat 120  
 gtcttcaaga atatatcatt cttttttcac tagaaccat tcaaaatata agtcaagaat 180  
 cttaatatca acaaatatat caagcaaact ggaaggcaga ataactacca taatttagta 240  
 taagtaccca aagttttata aatcaaaagc cctaatagata accattttta gaattcaatc 300  
 a 301

<210> 243  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 243  
 aggtaagtcc cagtttgaag ctcaaaagat ctggtatgag cataggctca tcgacgacat 60  
 ggtggcccaa gctatgaaat cagagggagg ctctcatctg gcctgtaaaa actatgatgg 120  
 tgacgtgcag tcggactctg tggcccaagg gtatggctct ctcggcata tgaccagcgt 180  
 gctggtttgt ccagatggca agacagtaga agcagaggct gccacaggga ctgtaaccgc 240  
 tcaactaccg atgttccaga aaggacagga gacgtccacc aatcccattg cttccatttt 300  
 t 301

<210> 244

<211> 300  
 <212> DNA  
 <213> Homo sapien

<400> 244  
 gctggtttgc aagaatgaaa tgaatgattc tacagctagg acttaacctt gaaatggaaa 60  
 gtcattgcaat cccattttgca ggatctgtct gtgcacatgc ctctgtagag agcagcattc 120  
 ccaggacact tggaaacagt tgacactgta aggtgcttgc tccccaaagac acatccctaaa 180  
 aggtgttgta atggtgaaaa cgtcttcctt ctttattgcc ccttcttatt tatgtgaaca 240  
 actggttgct ttttgtgtat cttttttaaa ctgtaaagtt caattgtgaa aatgaatatc 300

<210> 245  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 245  
 gtctgagtat ttaaaatggtt attgaaatta tccccaacca atgtagaaa agaaagaggt 60  
 tatatactta gataaaaaat gaggtgaatt actatccatt gaaatcatgc tcttagaatt 120  
 aaggccagga gatattgtca ttaatgtara cttcaggaca ctagagtata gcagccctat 180  
 gttttcaaag agcagagatg caattaaata ttgttttagca tcaaaaaggc cactcaatac 240  
 agctaataaa atgaaagacc taatttctaa agcaattctt tataattttac aaagttttaa 300  
 g 301

<210> 246  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 246  
 ggtctgtcct acaatgcctg cttcttgaaa gaagtcggca ctttctagaa tagctaaata 60  
 acctgggctt attttaaaga actatttgta gctcagattg gttttcctat ggctaaaata 120  
 agtgcttctt gtgaaaatta aataaaacag ttaattcaaa gccttgatat atgttaccac 180  
 taacaatcat actaaatata ttttgaagta caaagtttga catgctctaa agtgacaacc 240  
 caaatgtgtc ttacaaaaca cgttcctaac aaggtatgct ttacactacc aatgcagaaa 300  
 c 301

<210> 247  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 247  
 aggtcctttg gcagggtcga tggatcagag ctcaaactgg agggaaaggc atttcgggta 60  
 gcctaagagg gcgactggcg gcagcacaac caaggaaggc aaggttggtt cccccacgct 120  
 gtgtcctgtg ttcagggtcg acacacaatc ctcatgggaa caggatcacc catgcgctgc 180  
 ccttgatgat caaggttggg gcttaagtgg attaaggagg gcaagttctg gggttccttgc 240  
 cttttcaaac catgaagtca ggctctgtat ccctcctttt cctaactgat attctaacta 300  
 a 301

<210> 248  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 248  
 aggtccttgg agatgccatt tcagccgaag gactcttctw ttcggaagta caccctcact 60  
 attaggaaga ttcttagggg taatttttct gaggaaggag aactagccaa ctttaagaatt 120



acaggaagaa agtggtttgg aagacagcca aagaaataaa agcagattaa attgtatcag 180  
gtacattcca gcctgttggc aactccataa aaacatttca gattttaatc ccgaatttag 240  
ctaagagac tggatttttg ttttttatgt tgtgtgtcgc agagctaaaa actcagttcc 300  
c 301

<210> 249  
<211> 301  
<212> DNA  
<213> Homo sapien

<400> 249  
gtccagagga agcacctggg gctgaactag gcttgccctg ctgtgaactt gcacttggag 60  
ccctgacgct gctgttctcc ccgaaaaacc cgaccgacct ccgcgatctc cgtcccggcc 120  
ccaggagac acagcagtga ctacagagctg gtcgcacact gtgcctccct cctcaccgcc 180  
catcgtaatg aattattttg aaaattaatt caaccatcct ttcagattct ggatggaaag 240  
actgaatcct tgactcagaa ttgtttgctg aaaagaatga tgtgactttc ttagtcattt 300  
a 301

<210> 250  
<211> 301  
<212> DNA  
<213> Homo sapien

<400> 250  
ggtctgtgac aaggacttgc aggctgtggg aggcaagtga cccttaacac tacacttctc 60  
cttatcttta ttggcttgat aaacataatt atttctaaca ctactttatt tccagttgcc 120  
cataagcaca tcagtacttt tctctggctg gaatagtaaa cttaaagtatg gtacatctac 180  
ctaaaagact actatgtgga ataatacata ctaatgaagt attacatgat ttaaagacta 240  
caataaaacc aaacatgctt ataacattaa gaaaaacaat aaagatacat gattgaaacc 300  
a 301

<210> 251  
<211> 301  
<212> DNA  
<213> Homo sapien

<400> 251  
gccgaggtcc tacatttggc ccagtttccc cctgcacact ctccagggcc cctgcctcat 60  
agacaacctc atagagcata ggagaactgg ttgccctggg ggcaggggga ctgtctggat 120  
ggcaggggtc ctcaaaaatg ccactgtcac tgccaggaaa tgcttctgag cagtacacct 180  
cattgggatc aatgaaaagc ttcaagaaat cttcaggctc actctcttga aggcccgga 240  
cctctggagg ggggcagtgg aatcccagct ccaggacgga tcctgtcgaa aagatatcct 300  
c 301

<210> 252  
<211> 301  
<212> DNA  
<213> Homo sapien

<400> 252  
gcaaccaatc actctgtttc acgtgacttt tatcaccata caatttgtgg catttcctca 60  
ttttctacat tgtagaatca agagtgtaaa taaatgtata tcgatgtctt caagaatata 120  
tcattccttt ttacttagga acccattcaa aatataagtc aagaatctta atatcaacaa 180  
atatatcaag caaactggaa ggcagaataa ctaccataat ttagtataag taccctaaagt 240  
tttataaatc aaaagcccta atgataacca tttttagaat tcaatcatca ctgtagaatc 300  
a 301

<210> 253

<211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 253  
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 caactaaaaa aaaaaaataa agaaaaaatg tgctgcgttc tgaaaaataa ctcccttagct 120  
 tggctctgatt gttttcagac cttaaaatat aaacttggtt cacaagcttt aatccatgtg 180  
 gatttttttt cttagagAAC cacaaaacat aaaaggagca agtcggactg aatacctgtt 240  
 tccatagtgc ccacagggta ttcctcacat tttctccata ggaaatgct ttttcccaag 300  
 g 301

<210> 254  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 254  
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 aacttgacca attcccttga agcgggtggg ttaaaccctg taaatgggaa caaatccccc 120  
 ccaaatctct tcactttacc ctggtggact cctgactgta gaattttttg gttgaaacaa 180  
 gaaaaaata aagctttgga cttttcaagg ttgcttaaca ggtactgaaa gactggcctc 240  
 acttaaaactg agccaggaaa agctgcagat ttattaatgg gtgtgttagt gtgcagtggc 300  
 t 301

<210> 255  
 <211> 302  
 <212> DNA  
 <213> Homo sapien

<400> 255  
 agcttttttt tttttttttt tttttttttt ttcattaaaa aatagtgtctc tttattataa 60  
 attactgaaa tgtttctttt ctgaatataa atataaatat gtgcaaagt tgcattggat 120  
 tgggattttg ttgagttctt caagcatctc ctaataccct caagggcctg agtagggggg 180  
 aggaaaaagg actggagggtg gaatctttat aaaaaacaag agtgattgag gcagattgta 240  
 aacattatta aaaaacaaga acaaaacaaa aaaatagaga aaaaaaccac cccaacacac 300  
 aa 302

<210> 256  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)... (301)  
 <223> n = A,T,C or G

<400> 256  
 gttccagaaa acattgaagg tggttcccca aagtctaact agggataccc cctctagcct 60  
 aggaccctcc tccccacacc tcaatccacc aaaccatcca taatgcaccc agataggccc 120  
 acccccaaaa gcctggacac cttgagcaca cagttaatgc caggacagac tcactcttat 180  
 aggcaaatag ctgctggcaa actggcatta cctgggtttg ggggatgggg gggcaagtgt 240  
 gtggcctctc ggctgggtta gcaagaacat tcagggttagg cctaagttan tcgtgttagt 300  
 t 301

<210> 257  
 <211> 301

<212> DNA  
<213> Homo sapien

<400> 257  
gttgtggagg aactctggct tgctcattaa gtctactga ttttactat cccctgaatt 60  
tcccactta tttttgtctt tcaatatcgc aggccttaga agaggtctac ctgcctccag 120  
tcttacctag tccagtctac cccctggagt tagaatggcc atcctgaagt gaaaagtaat 180  
gtcacattac tcccttcagt gatttcttgt agaagtgcc atcctgaat gccaccaaga 240  
tcttaatctt cacatcttta atcttatctc tttgactcct ctttacaccg gagaaggctc 300  
c 301

<210> 258  
<211> 301  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(301)  
<223> n = A,T,C or G  
  
<400> 258  
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aggggccag ccaccaggcg cagaagcaag ataaacagta ggctcaagac cagagccacc 120  
cccagggcaa caagaatcca ataccaggac tgggcaaaat cttcaaagat cttaacactg 180  
atgtctcggg cattgaggct gtcaataana cgctgatccc ctgctgtatg gtggtgtcat 240  
tggtgatccc tgggagcgcc ggtggagtaa cgttggtcca tggaaagcag cgcccacaac 300  
t 301

<210> 259  
<211> 301  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(301)  
<223> n = A,T,C or G  
  
<400> 259  
tcatatatgc aaacaaatgc agactangcc tcaggcagag actaaaggac atctcttggg 60  
gtgtcctgaa gtgatttga cccctgaggg cagacaccta agtaggaatc ccagtgggaa 120  
gcaaaagccat aaggaagccc aggattcctt gtgatcagga agtggggccag gaaggctctgt 180  
tccagctcac atctcatctg catgcagcac ggaccggatg cgcccaactg gtcttggctt 240  
ccctcccatc ttctcaagca gtgtccttgt tgagccattt gcatccttgg ctccagggtg 300  
c 301

<210> 260  
<211> 301  
<212> DNA  
<213> Homo sapien

<400> 260  
ttttttttct ccctaaggaa aaagaaggaa caagtctcat aaaaccaa at aagcaatgg 60  
aaggtgtctt aacttgaaaa agattaggag tcaactgggtt acaagttata attgaatgaa 120  
agaactgtaa cagccacagt tggccatttc atgccaatgg cagcaaaaca caggattaac 180  
tagggcaaaa taaataagtg tgtggaagcc ctgataagtg cttaataaac agactgattc 240  
actgagacat cagtacctgc ccgggcggcc gctcgagccg aattctgcag atatccatca 300

c

301

<210> 261  
<211> 301  
<212> DNA  
<213> Homo sapien

<400> 261

aaatattcga gcaaatcctg taactaatgt gtctccataa aaggctttga actcagtga	60
tctgcttcca tccacgattc tagcaatgac ctctcggaca tcaaagctcc tcttaagggt	120
agcaccaact attccatata attcatcagc aggaaataaa ggctcttcag aagggttcaat	180
ggtgacatcc aatttcttct gataatttag attcctcaca accttcctag ttaagtgaag	240
ggcatgatga tcatccaaag cccagtgggc acttactcca gactttctgc aatgaagatc	300
a	301

<210> 262  
<211> 301  
<212> DNA  
<213> Homo sapien

<400> 262

gaggagagcc tggtacagca tttgtaagca cagaatactc caggagtatt tgtaattgtc	60
tgtgagcttc ttgccgcaag tctctcagaa atttaaaaag atgcaaattc ctgagtcacc	120
cctagacttc ctaaaccaga tcctctgggg ctggaacctg gcactctgca tttgtaatga	180
gggctttctg gtgcacacct aattttgtgc atctttgccc taaatcctgg attagtcccc	240
catcattacc cccacattat aatgggatag attcagagca gatactctcc agcaaagaat	300
c	301

<210> 263  
<211> 301  
<212> DNA  
<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(301)

<223> n = A,T,C or G

<400> 263

tttagcttgt ggtaaatgac tcacaaaact gattttaaaa tcaagttaat gtgaattttg	60
aaaattacta cttaatccta attcacaata acaatggcat taaggtttga cttgagttgg	120
ttcttagtat tatttatggg aaataggctc ttaccacttg caaataactg gccacatcat	180
taatgactga cttccagta aggctctcta aggggtaagt angaggatcc acaggatttg	240
agatgctaag gccccagaga tcgtttgatc caaccctctt attttcagag gggaaaatgg	300
g	301

<210> 264  
<211> 301  
<212> DNA  
<213> Homo sapien

<400> 264

aaagacgtta aaccactcta ctaccacttg tggaactctc aaagggtaaa tgacaaascc	60
aatgaatgac tctaaaaaca atatttacat ttaatggttt gtagacaata aaaaaacaag	120
gtggatagat ctagaattgt aacattttta gaaaaccata scatttgaca gatgagaaag	180
ctcaattata gatgcaaagt tataactaaa ctactatagt agtaaagaaa tacatttcac	240
acccttcata taaattcact atcttggctt gaggcactcc ataaaatgta tcacgtgcat	300
a	301

<210> 265  
<211> 301  
<212> DNA  
<213> Homo sapien

<400> 265  
tgcccaagtt atgtgtaagt gtatccgcac ccagaggtaa aactacactg tcattcttgt 60  
cttcttgtga cgcagtatct cttctctggg gagaagccgg gaagtcttct cctggctcta 120  
catattcttg gaagtctcta atcaactttt gttccatttg tttcatttct tcaggaggga 180  
ttttcagttt gtcaacatgt tctctaacaa cacttgccca tttctgtaaa gaatccaaag 240  
cagtccaagg ctttgacatg tcaacaacca gcataactag agtatccttc agagatacgg 300  
c 301

<210> 266  
<211> 301  
<212> DNA  
<213> Homo sapien

<400> 266  
taccgtctgc ctttctctcc atccaggcca tctgcgaatc tacatgggtc ctctattcgc 60  
acaccagatc actcttttct ctaccacag gcttgctatg agcaagagac acaaccttct 120  
ctcttctgtg ttccagcttc ttttctgtt ctccacccc cttaagttct attcctgggg 180  
atagagacac caatacccat aacctctctc ctaagcctcc ttataacca ggggtgcacag 240  
cacagactcc tgacaactgg taaggccaat gaactgggag ctccacagctg gctgtgcctg 300  
a 301

<210> 267  
<211> 301  
<212> DNA  
<213> Homo sapien

<400> 267  
aaagagcaca ggccagctca gcctgccctg gccatctaga ctccagcctg ctccatgggg 60  
gttctcagtg ctgagtcctt ccaggaaaag ctccacctaga ccttctgagg ctgaatcttc 120  
atctcagcag gcagcttctg agagcctgat attcctagcc ttgatgggtc ggagtaaagc 180  
ctcattctga ttctctctct tcttttcttt caagttggct ttctccacat ccctctgttc 240  
aattcgtctc agcttgtctg ctttagccct catttcaga agcttcttct ctttggcatc 300  
t 301

<210> 268  
<211> 301  
<212> DNA  
<213> Homo sapien

<400> 268  
aatgtctcac tcaactactt cccagcctac cgtggcctaa ttctgggagt tttcttctta 60  
gatcttggga gagctgggtc ttctaaggag aaggaggaag gacagatgta actttggatc 120  
tcgaagagga agtctaattg aagtaattag tcaacgggtc ttgttttagac tcttggata 180  
tgctgggtgg ctccagtggc ctttttggag aaagcaagta ttattcttaa ggagtaacca 240  
cttcccattg ttctactttc taccatcatc aattgtatat tatgtattct ttggagaact 300  
a 301

<210> 269  
<211> 301  
<212> DNA  
<213> Homo sapien

<400> 269  
 taacaatata cactagctat ctttttaact gtccatcatt agcaccaatg aagattcaat 60  
 aaaattacct ttattcacac atctcaaaac aattctgcaa attcttagtg aagtttaact 120  
 atagtcacag accttaata ttcacattgt tttctatgtc tactgaaaat aagttcacta 180  
 cttttctgga tattctttac aaaatcttat taaaattcct ggtattatca cccccaatta 240  
 tacagtagca caaccacctt atgtagtttt tacatgatag ctctgtagaa gtttcacatc 300  
 t 301

<210> 270  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 270  
 cattgaagag cttttgcgaa acatcagaac acaagtgcct ataaaattaa ttaagcctta 60  
 cacaagaata catattcctt ttatttctaa ggagttaaac atagatgtag ctgatgtggg 120  
 gagcttgctg gtgcagtgc tttggataa cactattcat ggccgaattg atcaagtcaa 180  
 ccaactcctt gaactggatc atcagaagaa ggggtgggca cgatatactg cactagataa 240  
 tggaccaacc aactaaattc tctcaccagg ctgtatcagt aaactggctt aacagaaaac 300  
 a 301

<210> 271  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc feature  
 <222> (1)...(301)  
 <223> n = A,T,C or G

<400> 271  
 aaaagggttct cataagatta acaatttaaa taaatatttg atagaacatt ctttctcatt 60  
 tttatagctc atcttttagg ttgatattca gtccatgcct cccttgctgt tcttgatcca 120  
 gaattgoaat cacttcatca gctgtattc gctccaattc tctataaagt ggggtccaagg 180  
 tgaaccacag agccacagca cacctctttc ccttggtgac tgccctcacc ccatganggt 240  
 tctctctcc agatganaac tgatcatgcg cccacatttt ggggtttata gaagcagtca 300  
 c 301

<210> 272  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 272  
 taaattgcta agccacagat aacaccaatc aaatggaaca aatcactgtc ttcaaagtgc 60  
 ttatcagaaa accaaatgag cctggaatct tcataatacc taaacatgcc gtatttagga 120  
 tccaataatt ccctcatgat gagcaagaaa aattctttgc gcacccctcc tgcattccca 180  
 gcatcttctc caacaaatat aaccttgagt ggcttcttgt aatctatgtt ctttgttttc 240  
 ctaaggactt ccattgcac tcctacaata ttttctctac gcaccactag aattaagcag 300  
 g 301

<210> 273  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<220>

<221> misc\_feature  
 <222> (1)...(301)  
 <223> n = A,T,C or G

<400> 273  
 acatgtgtgt atgtgtatct ttgggaaaan aanaagacat cttgtttayt atttttttgg 60  
 agagangctg ggacatggat aatcacwtaa tttgctayta tyactttaat ctgactygaa 120  
 gaaccgtcta aaaataaaat ttacatgctc dtatatctct tatagtatgc ttatttcacc 180  
 ttytttctgt ccagagagag tatcagtgac ananatttma ggggtgaamac atgmattggg 240  
 gggacttnty tttacngagm accctgcccg sgcgccctcg makcngantt ccgcsananc 300  
 t 301

<210> 274  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(301)  
 <223> n = A,T,C or G

<400> 274  
 cttatatact cttttctcaga ggcaaaagag gagatgggta atgtagacaa ttcttttgagg 60  
 aacagtaaatt gattattaga gagaangaat ggaccaagga gacagaaatt aacttgtaaa 120  
 tgattctctt tggaaatctga atgagatcaa gagggccagct ttagcttctg gaaaagtcca 180  
 tctaggtatg gttgcattct cgtcttcttt tctgcagtag ataatgaggt aaccgaaggc 240  
 aattgtgctt cttttgataa gaagctttct tggtcatac aggaaattcc aganaaagtc 300  
 c 301

<210> 275  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(301)  
 <223> n = A,T,C or G

<400> 275  
 teggtgtcag cagcacgtgg cattgaacat tgcaatgtgg agcccaaacc acagaaaatg 60  
 ggggtgaaatt ggccaacttt ctattaactt atgttggcaa ttttgccacc aacagtaagc 120  
 tggcccttct aataaaagaa aattgaaagg tttctcacta aacggaatta agtagtgag 180  
 tcaagagact cccaggcctc agcgtacctg cccgggcggc cgctcgaagc cgaattctgc 240  
 agatatccat cacactggcg gncgctcgan catgcatcta gaaggnccaa ttcgccctat 300  
 a 301

<210> 276  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 276  
 tgtacacata ctcaataaat aaatgactgc attgtggtat tattactata ctgattatat 60  
 ttatcatgtg acttctaatt agaaaatgta tccaaaagca aaacagcaga tatacaaaat 120  
 taaagagaca gaagatagac attaacagat aaggcaactt atacattgag aatccaaatc 180  
 caatacattt aaacatttgg gaaatgaggg ggacaaatgg aagccagatc aaatttgtgt 240

aaaactattc agtatgtttc ccttgcttca tgtctgagaa ggctctcctt caatggggat 300  
g 301

<210> 277  
<211> 301  
<212> DNA  
<213> Homo sapien  
  
<220>  
<221> misc\_feature  
<222> (1)...(301)  
<223> n = A,T,C or G

<400> 277  
tttgttgatg tcagtatttt attacttgcg ttatgagtgc tcacctggga aattctaaag 60  
atacagagga cttggaggaa gcagagcaac tgaatttaat ttaaaagaag gaaaacattg 120  
gaatcatggc actcctgata ctttcccaa tcaaacactct caatgccccca cctcgtcct 180  
caccatagtg gggagactaa agtggccacg gatttgcctt angtgtgcag tgcgttctga 240  
gttcnctgtc gattacatct gaccagtctc ctttttccga agtcnctccg ttcaatcttg 300  
c 301

<210> 278  
<211> 301  
<212> DNA  
<213> Homo sapien  
  
<220>  
<221> misc\_feature  
<222> (1)...(301)  
<223> n = A,T,C or G

<400> 278  
taccactaca ctccagcctg ggcaacagag caagacctgt ctcaaagcat aaaatggaat 60  
aacatatcaa atgaaacagg gaaaatgaag ctgacaattt atggaagcca gggcttgtca 120  
cagtctctac tgttattatg cattacctgg gaatttatat aagcccttaa taataatgcc 180  
aatgaacatc tcatgtgtgc tcacaatggt ctggcactat tataagtgtc tcacaggttt 240  
tatgtgttct tcgtaacttt atggantagg tactcggccg cgaacaacgt aagccgaatt 300  
c 301

<210> 279  
<211> 301  
<212> DNA  
<213> Homo sapien

<220>  
<221> misc\_feature  
<222> (1)...(301)  
<223> n = A,T,C or G

<400> 279  
aaagcaggaa tgcaaaagct tgcttttctg gtatgttcta ggtgtattgt gacttttact 60  
gttatattaa ttgccaatat aagtaaatat agattatata tgtatagtgt ttcacaaagc 120  
ttagaccttt accttccagc caccocacag tgcttgatat ttcagagtca gtcattgggt 180  
atacatgtgt agttccaaag cacataagct agaanaanaa atatttctag ggagcactac 240  
catctgtttt cacatgaaat gccacacaca tagaactoca acatcaattt cattgcacag 300  
a 301

<210> 280



<211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 280  
 ggtactggag ttttcctccc ctgtgaaaac gtaactactg ttgggagtga attgaggatg 60  
 tagaaagggtg gtggaaccaa attgtggtca atggaaatag gagaatatgg ttctcactct 120  
 tgagaaaaaa acctaagatt agcccaggta gttgcctgta acttcagttt ttctgcctgg 180  
 gtttgatata gtttaggggtt ggggttagat taagatctaa attacatcag gacaaagaga 240  
 cagactatta actccacagt taattaagga ggtatgttcc atgtttattt gttaaagcag 300  
 t 301

<210> 281  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 281  
 aggtacaaga aggggaatgg gaaagagctg ctgctgtggc attgttcaac ttggatattc 60  
 gccgagcaat ccaaaccctg aatgaagggg catcttctga aaaaggagat ctgaatctca 120  
 atgtggtagc aatggcttta tcgggttata cggatgagaa gaactccctt tggagagaaa 180  
 tgtgtagcac actgcgatta cagctaaata acccgatttt gtgtgtcatg ttgcatcttc 240  
 tgacaagtga aacaggatct tacgatggag ttttgtatga aaacaaagtt gcagtacctc 300  
 g 301

<210> 282  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 282  
 caggtactac agaattaaaa tactgacaag caagtagttt cttggcgtgc acgaattgca 60  
 tccagaaccc aaaaattaaag aaattcaaaa agacattttg tgggcacctg ctacacaga 120  
 agcgcagaag caaagcccag gcagaacat gctaaccctta cagctcagcc tgacagaag 180  
 cgcagaagca aagcccaggc agaaccatgc taaccttaca gctcagcctg cacagaagcg 240  
 cagaagcaaa gcccaggcag aacatgctaa ccttacagct cagcctgcac agaagcacag 300  
 a 301

<210> 283  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 283  
 atctgtatac ggcagacaaa ctttatarag tgtagagagg tgagcgaaag gatgcaaaag 60  
 cactttgagg gctttataat aatattgctgc ttgaaaaaaa aaatgtgtag ttgatactca 120  
 gtgcatctcc agacatagta aggggttgct ctgaccaatc aggtgatcat tttttctatc 180  
 acttcccagg ttttatgcaa aaattttgtt aaattctata atggtgatat gcattcttta 240  
 ggaaacatat acatttttaa aaattctatt tatgttaagaa ctgacagacg aatttgcttt 300  
 g 301

<210> 284  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 284  
 caggtacaaa acgctattaa gtggcttaga atttgaacat ttgtggtctt tatttacttt 60

```

gcttcgtgtg tgggcaaagc aacatcttcc ctaaatatat attaccaaga aaagcaagaa    120
gcagattagg tttttgacaa aacaaacagg ccaaaagggg gctgacctgg agcagagcat    180
ggtgagaggc aaggcatgag agggcaagtt tggtgtggac agatctgtgc ctactttatt    240
actggagtaa aagaaaacaa agttcattga tgtcgaagga tatatacagt gttagaaatt    300
a                                                                    301

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<210> 285
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

```

```

<400> 285
acatcaccat gatcggatcc cccacccatt atacgttgta tgtttacata aatactcttc    60
aatgatcatt agtggtttta aaaaaatact gaaaactcct tctgcatccc aatctctaac    120
caggaaagca aatgctatct acagacctgc aagccctccc tcaaacnaaa ctatttctgg    180
attaaatatg tctgacttct tttgaggtca cagcactagg caaatgctat ttacgatctg    240
caaaagctgt ttgaagagtc aaagcccca tgtgaacacg atttctggac cctgtaacag    300
t                                                                    301

```

```

<210> 286
<211> 301
<212> DNA
<213> Homo sapien

```

```

<400> 286
taccactgca ttccagcctg ggtgacagag tgagactccg tctccaaaaa aaactttgct    60
tgtatattat ttttgacctt cagtggatca ttctagtagg aaaggacagt aagatttttt    120
atcaaaatgt gtcattgccg taagagatgt tatattcttt tctcatttct tccccacca    180
aaaaaagct accatatagc ttataagtct caaatttttg ctttttacta aaatgtgatt    240
gtttctgttc attgtgtatg cttcatcacc tatattaggc aaattccatt ttttcccttg    300
t                                                                    301

```

```

<210> 287
<211> 301
<212> DNA
<213> Homo sapien

```

```

<400> 287
tacagatctg ggaactaaat attaaaaatg agtggtggctg gatatatgga gaatgttggg    60
cccagaagga acgtagagat cagatattac aacagctttg ttttgagggt tagaaatatg    120
aaatgatttg gttatgaacg cacagtttag gcagcagggc cagaatcctg accctctgcc    180
ccgtgggttat ctccctccca gcttggtctg ctcatgttat cacagtatc cattttgttt    240
gttgcatgtc ttgtgaagcc atcaagattt tctcgtctgt tttcctctca ttggtaatgc    300
t                                                                    301

```

```

<210> 288
<211> 301
<212> DNA
<213> Homo sapien

```

```

<400> 288
gtacacctaa ctgcaaggac agctgaggaa tgtaatgggc agccgctttt aaagaagtag    60
agtcaatagg aagacaaatt ccagttccag ctcagtctgg gtatctgcaa agctgcaaaa    120

```

```

gatcttttaa gacaatttca agagaatatt tccttaaagt tggcaatttg gagatcatatc 180
aaaagcatct gcttttgtga tttaatttag ctcatctggc cactggaaga atccaaacag 240
tctgccttaa ttttgatga atgcatgatg gaaattcaat aatttagaaa gttaaaaaaa 300
a 301

```

```

<210> 289
<211> 301
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

```

```

<400> 289
ggtacactgt ttccatgta tgtttctaca cattgctacc tcagtgtcc tggaaactta 60
gcttttgatg tctccaagta gtccaccttc atttaactct ttgaaactgt atcatctttg 120
ccaagtaaga gtggtggcct atttcagctg ctttgacaaa atgactggct cctgacttaa 180
cgttctataa atgaatgtgc tgaagcaaag tgcccatggt ggccggcgaan aagagaaaga 240
tgtgtttgt tttgactct ctgtggtccc ttccaatgct gtgggtttcc aaccagnnga 300
a 301

```

```

<210> 290
<211> 301
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

```

```

<400> 290
acactgagct cttcttgata aatatacaga atgcttggca tatacaagat tctatactac 60
tgactgatct gtccatttct ctccacagctc ttaccccaa aagcttttcc accctaagt 120
ttctgacctc cttttctaata cacagtaggg atagaggcag anccacctac aatgaacatg 180
gagttctatc aagaggcaga aacagcacag aatcccagtt ttaccattcg ctgacagtgc 240
tgcttgaac aaaaacattt ctccatgtct cattttcttc atgectcaag taacagtga 300
a 301

```

```

<210> 291
<211> 301
<212> DNA
<213> Homo sapien

```

```

<400> 291
caggtaccaa tttcttctat cctagaaaca tttcatttta tgttggtgaa acataacaac 60
tatacagct agattttttt tctatgcttt acctgctatg gaaaatttga cacattctgc 120
tttactcttt tgtttatagg tgaatcacia aatgtatttt tatgtattct gtagttcaat 180
agccatggct gtttacttca tttaatttat ttagcataaa gacattatga aaaggcctaa 240
acatgagctt cacttcccca ctaactaatt agcatctgtt atttcttaac cgtaatgcct 300
a 301

```

```

<210> 292
<211> 301
<212> DNA
<213> Homo sapien

```

<220>  
 <221> misc\_feature  
 <222> (1)...(301)  
 <223> n = A,T,C or G

<400> 292  
 accttttagt agtaatgtct aataataaat aagaaatcaa ttttataagg tccatatagc 60  
 tgtattaaat aatttttaag tttaaaagat aaaataccat catttttaat gttgggtattc 120  
 aaaaccaaag natataaccg aaaggaaaaa cagatgagac ataaaatgat ttgcnagatg 180  
 ggaaatatag tasttyatga atgttnatta aattccagtt ataatagtgg ctacacactc 240  
 tcactacaca cacagacccc acagtcctat atgccacaaa cacattttcca taacttgaaa 300  
 a 301

<210> 293  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 293  
 ggtaccaagt gctgggtgcca gcctgttacc tgttctcact gaaaagtctg gctaattgctc 60  
 ttgtgtagtc acttctgatt ctgacaatca atcaatcaat ggcctagagc actgactggt 120  
 aacacaaaag tcaactagcaa agtagcaaca gctttaagtc taaatacaaa gctgttctgt 180  
 gtgagaattt tttaaaaggc tacttgtata ataacccttg tcatttttaa tgtacctcgg 240  
 ccgcgaccac gctaagccga attctgcaga tatccatcac actggcgggc gctcgagcat 300  
 g 301

<210> 294  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(301)  
 <223> n = A,T,C or G

<400> 294  
 tgacccataa caatatacac tagctatctt ttttaactgtc catcattagc accaatgaag 60  
 attcaataaa attaccttta ttcacacatc tcaaaaacat tctgcaaat cttagtgaag 120  
 ttttaactata gtcacaganc ttaaattatc acattgtttt ctatgtctac tgaaaataag 180  
 ttcactactt ttctgggata ttctttacaa aatcttatta aaattcctgg tattatcacc 240  
 cccaattata cagtagcaca accaccttat gtagttttta catgatagct ctgtagagggt 300  
 t 301

<210> 295  
 <211> 305  
 <212> DNA  
 <213> Homo sapien

<400> 295  
 gtactctttc tctccctcc tctgaattta attctttcaa cttgcaattt gcaaggatta 60  
 cacatttcac tgtgatgtat attgtgttgc aaaaaaaaaa gtgtctttgt ttaaaattac 120  
 ttggtttgty aatccatctt gctttttccc cattggaact agtcattaac ccatctctga 180  
 actggtagaa aaacrtctga agagctagtc tatcagcatc tgacagggtga attggatggg 240  
 tctcagaacc atttcaccca gacagcctgt ttctatcctg ttttaataaat tagtttgggg 300  
 tctct 305

<210> 296  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 296  
 aggtactatg ggaagctgct aaaataatat ttgatagtaa aagtatgtaa tgtgctatct 60  
 caccctagtag taaactaaaa ataaactgaa actttatgga atctgaagtt attttccttg 120  
 attaaataga attaataaac caatatgagg aaacatgaaa ccatgcaatc tactatcaac 180  
 ttgaaaaag tgattgaacg aaccacttag ctttcagatg atgaacactg ataagtcatt 240  
 tgtcattact ataaatttta aaatctgtta ataagatggc ctatagggag gaaaaagggg 300  
 c 301

<210> 297  
 <211> 300  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(300)  
 <223> n = A,T,C or G

<400> 297  
 actgagtttt aactggacgc caagcaggca aggctggaag gttttgctct ctttgtgcta 60  
 aaggttttga aaaccttgaa ggagaatcat ttgacaaga agtacttaag agtctagaga 120  
 acaaagangt gaaccagctg aaagctctcg gggaanctt acatgtgttg ttaggcctgt 180  
 tccatcattg ggagtgcact ggccatccct caaaatttgt ctgggctggc ctgagtggc 240  
 accgcacctc ggcgcgacc acgctaagcc gaattctgca gatatccatc aactggcgg 300

<210> 298  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(301)  
 <223> n = A,T,C or G

<400> 298  
 tatgggggttt gtcacccaaa agctgatgct gagaaaggcc tccctggggc ccctcccgcg 60  
 ggcatctgag agacctggtg ttccagtgtt tctggaaatg ggtcccagtg ccgccggctg 120  
 tgaagctctc agatcaatca cggaagggc ctggcgggtg tggccacctg gaaccaccct 180  
 gtctgtctg tttacatttc actaycaggt tttctctggg cattacnatt tgttccccta 240  
 caacagtgac ctgtgcattc tgctgtggcc tgctgtgtct gcagggtggc ctcagcgagg 300  
 t 301

<210> 299  
 <211> 301  
 <212> DNA  
 <213> Homo sapien

<400> 299  
 gttttgagac ggagtttcac tcttgttgcc cagactggac tgcaatggca gggctctctgc 60  
 tcaactgcacc ctctgcctcc caggttcgag caattctcct gcctcagcct ccaggttagc 120  
 tgggattgca ggctcacgcc accataccca gctaattttt ttgtattttt agtagagacg 180  
 gagtttcgcc atgttgcca gctggctcga aactcctgac ctcaagcgac ctgcctgcct 240

cggcctccca aagtgcctgga attataggca tgagtcaaca cgcccagcct aaagatatatt 300  
t 301

<210> 300  
<211> 301  
<212> DNA  
<213> Homo sapien

<400> 300  
attcagtttt atttgcctgcc ccagtatctg taaccaggag tgccacaaaa tcttgccaga 60  
tatgtcccac acccactggg aaaggctccc acctggtac ttctctatc agctgggtca 120  
gctgcattcc acaaggttct cagcctaatt agtttacta cctgccagtc tcaaaactta 180  
gtaaagcaag accatgacat tccccacgg aaatcagagt ttgccccacc gtcttgttac 240  
tataaagcct gcctctaaca gtcttgctt cttcacacca atcccgagcg catcccccat 300  
g 301

<210> 301  
<211> 301  
<212> DNA  
<213> Homo sapien

<400> 301  
ttaaattttt gagaggataa aaaggacaaa taatctagaa atgtgtcttc ttcagctcgc 60  
agaggacccc aggtctccaa gcaaccacat ggtcaagggc atgaataatt aaaagttggt 120  
gggaactcac aaagacctc agagctgaga caccacaac agtgggagct cacaagacc 180  
ctcagagctg agacaccac aacagtggga gctcacaag acctcagag ctgagacacc 240  
cacaacagca cctcgttcag ctgccacatg tgtgaataag gatgcaatgt ccagaagtgt 300  
t 301

<210> 302  
<211> 301  
<212> DNA  
<213> Homo sapien

<400> 302  
aggtaacacat ttagcttgtg gtaaattgact cacaaaactg attttaaaat caagttaatg 60  
tgaattttga aaattactac ttaattcctaa ttcacaataa caatggcatt aaggtttgac 120  
ttgagttggt tottagtatt atttatggta aataggctct taccacttgc aaataactgg 180  
ccacatcatt aatgactgac ttcccagtaa ggctctctaa ggggtaagta ggaggatcca 240  
caggatttga gatgctaagg ccccagagat cgtttgatcc aaccctctta ttttcagagg 300  
g 301

<210> 303  
<211> 301  
<212> DNA  
<213> Homo sapien

<400> 303  
aggtaaccaac tgtggaaata ggtagaggat ctttttttct ttccatatca actaagttgt 60  
atattgtttt ttgacagttt aacacatctt cttctgtcag agattcttct acaatagcac 120  
tggtaatgg aactaccgct tgcatgttaa aaatgggtgt ttgtgaaatg atcataggcc 180  
agtaacgggt atgtttttct aactgatctt ttgctcgttc caaagggacc tcaagacttc 240  
catcgatttt atatctgggg tctagaaaag gagttaatct gttttccctc ataaattcac 300  
c 301

<210> 304  
<211> 301  
<212> DNA

<213> Homo sapien

<400> 304

acatggatgt tatTTTgcag actgtcaacc tgaatttTga tttgcttgac attgcctaatt	60
tattagtttc agtttcagct taccactttt ttgtctgcaa catgcaraas agacagtgcc	120
cttttttagtg tatcatatca ggaatcatct cacattgggtt tgtgccatta ctggtgcagt	180
gactttcagc cacttgggta aggtggagtt ggccatatgt ctccactgca aaattactga	240
ttttcctttt gtaattaata agtgtgtgtg tgaagattct ttgagatgag gtatatatct	300
c	301

<210> 305

<211> 301

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(301)

<223> n = A,T,C or G

<400> 305

gangtacagc gtggtcaagg taacaagaag aaaaaaatgt gagtggcatc ctgggatgag	60
cagggggaca gacctggaca gacacgttgt catttgctgc tgtgggtagg aaaatgggag	120
taaaggagga gaaacagata caaatctcc aactcagtat taaggatttc tcatgcctag	180
aatattggta gaaacaagaa tacattcata tggcaaataa ctaacctatg tggaacaaaa	240
ttctgggatt taagttggat accaangaaa ttgtattaaa agagctgttc atggaataag	300
a	301

<210> 306

<211> 8

<212> PRT

<213> Homo sapien

<400> 306

Val Leu Gly Trp Val Ala Glu Leu
1 5

<210> 307

<211> 637

<212> DNA

<213> Homo sapien

<400> 307

acaggggratg aagggaaagg gagaggatga ggaagccccc ctggggattt ggtttgggcc	60
ttgtgatcag gtggtctatg gggcttatcc ctacaaagaa gaatccagaa ataggggcac	120
attgaggaat gatacttgag cccaaagagc attcaatcat tgttttattt gccttmtttt	180
cacaccattg gtgaggagg gattaccacc ctgggggttat gaagatggtt gaacacccca	240
cacatagcac cggagatatg agatcaacag tttcttagcc atagagattc acagcccaga	300
gcaggaggac gcttgacac catgcaggat gacatggggg atgcgctcgg gattggtgtg	360
aagaagcaag gactgttaga ggcaggcttt atagtaacaa gacggtgggg caaactctga	420
tttccgtggg ggaatgtcat ggtcttgctt tactaagttt tgagactggc aggtagtga	480
actcattagg ctgagaacct tgtggaatgc acttgaccca sctgatagag gaagtagcca	540
ggtgggagcc tttcccagtg ggtgtgggac atatctggca agattttgtg gcactcctgg	600
ttacagatac tggggcagca aataaaactg aatcttg	637

<210> 308

<211> 647

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature

<222> (1)...(647)

<223> n = A,T,C or G

<400> 308

acgattttca	ttatcatgta	aatcgggtca	ctcaaggggc	caaccacagc	tgggagccac	60
tgctcagggg	aaggttcata	tgggactttc	tactgcccaa	ggttctatac	aggatataaa	120
ggngcctcac	agtatagatc	tggtagcaaa	gaagaagaaa	caaacactga	tctctttctg	180
ccaccctct	gacccttttg	aactcctctg	accctttaga	acaagcctac	ctaatatctg	240
ctagagaaaa	gaccaacaac	ggcctcaaag	gatctcttac	catgaaggtc	tcagctaatt	300
cttggctaag	atgtgggttc	cacattaggt	tctgaatatg	gggggaagg	tcaatttgct	360
cattttgtgt	gtggataaag	tcaggatgcc	caggggccag	agcagggggc	tgcttgcttt	420
gggaacaatg	gctgagcata	taaccatagg	ttatggggaa	caaaacaaca	tcaaagtcac	480
tgtatcaatt	gccatgaaga	cttgagggac	ctgaatctac	cgattcatct	taaggcagca	540
ggaccagttt	gagtggcaac	aatgcagcag	cagaatcaat	ggaaacaaca	gaatgattgc	600
aatgtccttt	tttttctcct	gcttctgact	tgataaaagg	ggaccgt		647

<210> 309

<211> 460

<212> DNA

<213> Homo sapien

<400> 309

actttatagt	ttaggctgga	cattggaaaa	aaaaaaaagc	cagaacaaca	tgtgatagat	60
aatatgattg	gctgcacact	tccagactga	tgaatgatga	acgtgatgga	ctattgtatg	120
gagcacatct	tcagcaagag	ggggaataac	tcacattttt	tggccagcag	ttgtttgatc	180
accaaacatc	atgccagaat	actcagcaaa	ccttcttagc	tcttgagaag	tcaaagtccg	240
ggggaattta	ttcctggcaa	ttttaattgg	actccttatg	tgagagcagc	ggctaccag	300
ctggggtggt	ggagcgaacc	cgtcactagt	ggacatgcag	tggcagagct	cctggtaacc	360
acctagagga	atacacaggc	acatgtgtga	tgccaagcgt	gacacctgta	gcactcaaat	420
ttgtcttggt	tttgtctttc	ggtgtgtaag	attcttaagt			460

<210> 310

<211> 539

<212> DNA

<213> Homo sapien

<400> 310

acgggactta	tcaaataaag	ataggaaaag	aagaaaactc	aaatattata	ggcagaaatg	60
ctaaagggtt	taaaatatgt	caggattgga	agaaggcatg	gataaagaac	aaagttcagt	120
taggaaagag	aaacacagaa	ggaagagaca	caataaaaagt	cattatgtat	tctgtgagaa	180
gtcagacagt	aagattttgt	ggaaatgggt	tggtttggtg	tatggtagat	attttagcaa	240
taatctttat	ggcagagaaa	gctaaaatcc	tttagcttgc	gtgaatgatc	acttgctgaa	300
ttcctcaagg	taggcatgat	gaaggagggt	ttagaggaga	cacagacaca	atgaactgac	360
ctagatagaa	agccttagta	tactcagcta	ggaatagtga	ttctgagggc	acactgtgac	420
atgattatgt	cattacatgt	atggtagtga	tggggatgat	aggaagggaag	aacttatggc	480
atattttcac	ccccacaaaa	gtcagttaaa	tattgggaca	ctaaccatcc	aggtcaaga	539

<210> 311

<211> 526

<212> DNA

<213> Homo sapien

<220>

<221> misc\_feature



&lt;222&gt; (1)... (526)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 311

caaatttgag ccaatgacat agaattttac aaatcaagaa gcttattctg gggccatttc	60
ttttgacgtt ttctctaaac tactaaagag gcattaatga tccataaatt atattatcta	120
catttacagc atttaaaatg tggtcagcat gaaatattag ctacagggga agctaaataa	180
attaaacatg gaataaagat ttgtccttaa atataatcta caagaagact ttgatatttg	240
tttttcacaa gtgaagcatt cttataaagt gtcataacct ttttggggaa actatgggaa	300
aaaatgggga aactctgaag ggttttaagt atcttacctg aagctacaga ctccataacc	360
tctctttaca gggagctcct gcagccctca cagaaatgag tggctgagat tcttgattgc	420
acagcaagag cttctcatct aaaccctttc cttttttagt atctgtgtat caagtataaa	480
agttctataa actgtagtnt acttatttta atccccaaag cacagt	526

&lt;210&gt; 312

&lt;211&gt; 500

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)... (500)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 312

cctctctctc cccacccct gactctagag aactggggtt tctcccagta ctccagcaat	60
tcatttctga aagcagttga gccactttat tccaaagtac actgcagatg ttcaaactct	120
ccatttctct ttccctcca cctgccagtt ttgctgactc tcaacttgct atgagtgtaa	180
gcattaagga cattatgctt cttcgattct gaagacaggc cctgctcatg gatgactctg	240
gcttcttagg aaaatatttt tcttccaaaa tcagtaggaa atctaaactt atccccctct	300
tgcatagtc tagcagcttc agacatttgg ttaagaacct atgggaaaaa aaaaaatcct	360
tgctaattgt gtttcctttg taaaccanga ttcttatttg nctggtatag aatatcagct	420
ctgaacgtgt ggtaaagatt tttgtgtttg aatataggag aaatcagttt gctgaaaagt	480
tagttttaat tatctattgg	500

&lt;210&gt; 313

&lt;211&gt; 718

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)... (718)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 313

ggagatttgt gtggtttgca gccgaggag accaggaaga tctgcatggt gggaaggacc	60
tgatgataca gaggtgagaa ataagaaagg ctgctgactt taccatctga ggccacacat	120
ctgctgaaat ggagataatt aacatcacta gaaacagcaa gatgacaata taatgtctaa	180
gtagtgacat gtttttgac atttccagcc cttttaaata tccacacaca caggaagcac	240
aaaaggagac acagagatcc ctgggagaaa tgcccggccg ccactctggg tcatcgatga	300
gcctcgccct gtgcctgntc ccgcttgatg gggaaggaca ttagaaaatg aattgatgtg	360
ttccttaaaag gatggcagga aaacagatcc tgggtgtgat atttatttga acgggattac	420
agatttgaaa tgaagtcaca aagtgagcat taccatgag aggaaaacag acgagaaaat	480
cttgatggtt cacaagacat gcaacaaaca aaatggaata ctgtgatgac acgagcagcc	540
aactggggag gagataccac ggggcagagg tcaggattct ggccctgctg cctaactgtg	600
cgttatacca atcatttcta tttctaccct caaacaagct gtngaatatc tgacttacgg	660
ttctnttngc ccacattttc atnatccacc ccntcntttt aannttantc caaantgt	718

<210> 314  
 <211> 358  
 <212> DNA  
 <213> Homo sapien

<400> 314  
 gtttattttac attacagaaa aaacatcaag acaatgtata ctattttcaaa tatatccata 60  
 cataatcaaa tatagctgta gtacatgttt tcattgggtg agattaccac aaatgcaagg 120  
 caacatgtgt agatctcttg tcttattctt ttgtctataa tactgtattg tgtagtccaa 180  
 gctctcggtg gtccagccac tgtgaaacat gtcaccttta gattaacctc gtggacgctc 240  
 ttgttgtatt gctgaactgt agtgccctgt attttgcttc tgtctgtgaa ttctgttgct 300  
 tctggggcat ttcttgtga tgcagaggac caccacacag atgacagcaa tctgaatt 358

<210> 315  
 <211> 341  
 <212> DNA  
 <213> Homo sapien

<400> 315  
 taccacctcc ccgctggcac tgatgagccg catcaccatg gtcaccagca ccatgaaggc 60  
 ataggtgatg atgaggacat ggaatgggcc cccaaggatg gtctgtccaa agaagcagat 120  
 gaccccatc ctgaagatgt ctggaacctc taccagcagg atgatgatag cccaatgac 180  
 agtcaccagc tccccgacca gccggatata gtccctaggg gtcatgtagg ctctctgaag 240  
 tagcttctgc tgtaagaggg tgttgtcccg ggggctcgtg cggttattgg tcctgggctt 300  
 gagggggcgg tagatgcagc acatggtgaa gcagatgatg t 341

<210> 316  
 <211> 151  
 <212> DNA  
 <213> Homo sapien

<400> 316  
 agactgggca agactcttac gccccacact gcaatttggc cttgttgccg tatccattta 60  
 tgtgggcctt tctcgagttt ctgattataa acaccactgg agcagatgtg tgactggact 120  
 cattcaggga gctctgggtg caatattagt t 151

<210> 317  
 <211> 151  
 <212> DNA  
 <213> Homo sapien

<400> 317  
 agaactagtg gatcctaag aaataacctga aacatatatt ggcattttatc aatggctcaa 60  
 atcttcattt atctctggcc ttaacctggg ctctgaggc tgcggccagc agatcccagg 120  
 ccagggtctt gttcttgcca cacctgctt a 151

<210> 318  
 <211> 151  
 <212> DNA  
 <213> Homo sapien

<400> 318  
 actggtggga ggcgctgttt agttggctgt ttccagaggg gtctttcgga gggacctctc 60  
 gctgcaggct ggagtgtctt tattctggc gggagaccgc acattccact gctgaggctg 120  
 tgggggcggg ttatcaggca gtgataaaca t 151

<210> 319

<211> 151  
 <212> DNA  
 <213> Homo sapien

<400> 319  
 aactagtggg tccagagcta taggtacagt gtgatctcag ctttgcaaac acattttcta 60  
 catagatagt actaggtatt aatagatatg taaagaaaga aatcacacca ttaataatgg 120  
 taagattggg tttatgtgat tttagtgggt a 151

<210> 320  
 <211> 150  
 <212> DNA  
 <213> Homo sapien

<400> 320  
 aactagtggg tccactagtc cagtgtgggt gaattccatt gtgttggggt tctagatcgc 60  
 gagcggctgc cctttttttt tttttttttg ggggggaatt tttttttttt aatagttatt 120  
 gagtgttcta cagcttacag taaataccat 150

<210> 321  
 <211> 151  
 <212> DNA  
 <213> Homo sapien

<400> 321  
 agcaactttg tttttcatcc aggttatattt aggccttagga tttcctctca cactgcagtt 60  
 taggggtggc ttgtaaccag ctatggcata ggtgttaacc aaaggctgag taaacatggg 120  
 tgcctctgag aaatcaaagt cttcatacac t 151

<210> 322  
 <211> 151  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(151)  
 <223> n = A,T,C or G

<400> 322  
 atccagcatc ttctcctggt tcttgccctc ctttttcttc ttcttasatt ctgcttgagg 60  
 tttgggcttg gtcagtttgc cacagggctt ggagatgggt acagctcttc gccattcggc 120  
 attgtgcagg gctcgttcca nacttcagtt t 151

<210> 323  
 <211> 151  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(151)  
 <223> n = A,T,C or G

<400> 323  
 tgaggacttg tktttttttt ctttatattt aatcctctta ckttgtaaatt atattgccta 60  
 nagactcant tactaccag tttgtggtt twtgggagaa atgtaactgg acagttagct 120  
 gttcaatyaa aaagacactt ancccatgtg g 151

<210> 324  
 <211> 461  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(461)  
 <223> n = A,T,C or G

<400> 324  
 acctgtgtgg aatttcagct ttctcatgc aaaaggattt tgtatccccg gcctacttga 60  
 agaagtgggc agctaaagga atccagggtg ttggttgac tgtaataacc ttgatgaaa 120  
 agagttacta cgaatcccat cttggttcca gctatatcac tgacagcatg gtagaagact 180  
 gcgaacctca cttctagact ttcacgggtg gacgaaacgg gttcagaaac tgccaggggc 240  
 ctcatcacagg gatatcaaaa taccctttgt gctaccagg ccctggggaa tcagggtgact 300  
 cacacaaatg caatagttgg tcaactgcatt tttaactgaa ccaaagctaa acccggtgtt 360  
 gccaccatgc accatggcat gccagagttc aacactgttg ctcttgaaaa ttgggtctga 420  
 aaaaacgcac aagagcccct gccctgccct agctgangca c 461

<210> 325  
 <211> 400  
 <212> DNA  
 <213> Homo sapien

<400> 325  
 acactgtttc catgttatgt ttctacacat tgctacctca gtgctcctgg aaacttagct 60  
 tttgatgtct ccaagtagtc caccttcatt taactctttg aaactgtatc atctttgcc 120  
 agtaagagtg gtggcctatt tcagctgctt tgacaaaatg actggctcct gacttaacgt 180  
 tctataaatg aatgtgctga agcaaagtgc ccatgggtggc ggcaagaag agaaagatgt 240  
 gttttgtttt ggactctctg tggctccctc caatgctgtg ggtttccaac caggggaagg 300  
 gtcccttttg cattgccaag tgccataacc atgagcacta cgctaccatg gttctgcctc 360  
 ctggccaagc aggttggttt gcaagaatga aatgaatgat 400

<210> 326  
 <211> 1215  
 <212> DNA  
 <213> Homo sapien

<400> 326  
 ggaggactgc agcccgcact cgcagccctg gcaggcggca ctggtcatgg aaaacgaatt 60  
 gttctgctcg ggcgtcctgg tgcacccgca gtgggtgctg tcagccgcac actgtttcca 120  
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 <212> PRT  
 <213> Homo sapien

<400> 327

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Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu Gly
          35          40          45
Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val Glu
          50          55          60
Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu Leu Ala
          65          70          75          80
Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser Asp
          85          90          95
Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly Asn
          100          105          110
Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg Met Pro
          115          120          125
Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu Glu Val Cys
          130          135          140
Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys Ala Gly
          145          150          155          160
Gly Gly Gln Asp Gln Lys Asp Ser Cys Asn Gly Asp Ser Gly Gly Pro
          165          170          175
Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly Lys Ala
          180          185          190
Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn Leu Cys Lys
          195          200          205
Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
          210          215          220

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<210> 328  
 <211> 234  
 <212> DNA  
 <213> Homo sapien

<400> 328

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<210> 329  
 <211> 77  
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 <213> Homo sapien

<400> 329

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105

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 Phe Cys Ser Gly Val Leu Val His Pro Gln Trp Val Leu Ser Ala Thr  
                     35                      40                      45  
 His Cys Ser Gln Asn Ser Tyr Thr Ile Gly Leu Gly Leu His Ser Leu  
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 <212> PRT  
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 <212> DNA  
 <213> Homo sapien

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&lt;211&gt; 3030

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 333

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&lt;211&gt; 2417

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 334

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&lt;210&gt; 335

&lt;211&gt; 2984

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 335

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<210> 336  
 <211> 147  
 <212> PRT  
 <213> Homo sapien

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<400> 336
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Leu Asp Ser Glu Asn Thr Ser Gly Ala Leu Pro Arg Leu Pro Gln Thr
20          25          30
Pro Lys Gln Pro Gln Lys Arg Ser Arg Ala Ala Phe Ser His Thr Gln
35          40          45
Val Ile Glu Leu Glu Arg Lys Phe Ser His Gln Lys Tyr Leu Ser Ala
50          55          60
Pro Glu Arg Ala His Leu Ala Lys Asn Leu Lys Leu Thr Glu Thr Gln
65          70          75          80
Val Lys Ile Trp Phe Gln Asn Arg Arg Tyr Lys Thr Lys Arg Lys Gln
85          90          95
Leu Ser Ser Glu Leu Gly Asp Leu Glu Lys His Ser Ser Leu Pro Ala
100         105         110
Leu Lys Glu Glu Ala Phe Ser Arg Ala Ser Leu Val Ser Val Tyr Asn
115         120         125
Ser Tyr Pro Tyr Tyr Pro Tyr Leu Tyr Cys Val Gly Ser Trp Ser Pro
130         135         140
Ala Phe Trp
145

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<210> 337  
 <211> 9  
 <212> PRT  
 <213> Homo sapien

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<400> 337
Ala Leu Thr Gly Phe Thr Phe Ser Ala
1          5

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<210> 338  
 <211> 9  
 <212> PRT  
 <213> Homo sapien

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<400> 338
Leu Leu Ala Asn Asp Leu Met Leu Ile
1          5

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<210> 339  
 <211> 318

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 339

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Met Val Glu Leu Met Phe Pro Leu Leu Leu Leu Leu Leu Pro Phe Leu
 1          5          10          15
Leu Tyr Met Ala Ala Pro Gln Ile Arg Lys Met Leu Ser Ser Gly Val
          20          25          30
Cys Thr Ser Thr Val Gln Leu Pro Gly Lys Val Val Val Val Thr Gly
          35          40          45
Ala Asn Thr Gly Ile Gly Lys Glu Thr Ala Lys Glu Leu Ala Gln Arg
          50          55          60
Gly Ala Arg Val Tyr Leu Ala Cys Arg Asp Val Glu Lys Gly Glu Leu
65          70          75          80
Val Ala Lys Glu Ile Gln Thr Thr Thr Gly Asn Gln Gln Val Leu Val
          85          90          95
Arg Lys Leu Asp Leu Ser Asp Thr Lys Ser Ile Arg Ala Phe Ala Lys
          100          105          110
Gly Phe Leu Ala Glu Glu Lys His Leu His Val Leu Ile Asn Asn Ala
          115          120          125
Gly Val Met Met Cys Pro Tyr Ser Lys Thr Ala Asp Gly Phe Glu Met
130          135          140
His Ile Gly Val Asn His Leu Gly His Phe Leu Leu Thr His Leu Leu
145          150          155          160
Leu Glu Lys Leu Lys Glu Ser Ala Pro Ser Arg Ile Val Asn Val Ser
          165          170          175
Ser Leu Ala His His Leu Gly Arg Ile His Phe His Asn Leu Gln Gly
          180          185          190
Glu Lys Phe Tyr Asn Ala Gly Leu Ala Tyr Cys His Ser Lys Leu Ala
          195          200          205
Asn Ile Leu Phe Thr Gln Glu Leu Ala Arg Arg Leu Lys Gly Ser Gly
210          215          220
Val Thr Thr Tyr Ser Val His Pro Gly Thr Val Gln Ser Glu Leu Val
225          230          235          240
Arg His Ser Ser Phe Met Arg Trp Met Trp Trp Leu Phe Ser Phe Phe
          245          250          255
Ile Lys Thr Pro Gln Gln Gly Ala Gln Thr Ser Leu His Cys Ala Leu
          260          265          270
Thr Glu Gly Leu Glu Ile Leu Ser Gly Asn His Phe Ser Asp Cys His
          275          280          285
Val Ala Trp Val Ser Ala Gln Ala Arg Asn Glu Thr Ile Ala Arg Arg
290          295          300
Leu Trp Asp Val Ser Cys Asp Leu Leu Gly Leu Pro Ile Asp
305          310          315

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&lt;210&gt; 340

&lt;211&gt; 483

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 340

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gccgaggtct gccttcacac ggaggacacg agactgcttc ctcaagggct cctgcctgcc      60
tggaactgg tgggagcgc tgttagttg gctgtttca gaggggtctt tcggaggac      120
ctctgctgc aggtggagt gtctttatc ctggcgggag accgcacatt ccaactgctga      180
ggttggtggg gcggtttatc aggcagtgat aaacataaga tgtcatttcc ttgactccgg      240
ccttcaattt tctctttggc tgacgacgga gtccgtggtg tcccgatgta actgaccct      300
gctccaaacg tgacatcact gatgctcttc tcgggggtgc tgatggcccg cttggtcacg      360
tgctcaatct cgccattcga ctcttgctcc aaactgtatg aagacacctg actgcacgtt      420

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ctg	483

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 <211> 344  
 <212> DNA  
 <213> Homo sapien

<400> 341	
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tatttttact aaccattcta tttttataga aatagctgag agtttctaaa ccaactctct	120
gctgccttac aagtattaaa tattttactt ctttccataa agagtagctc aaaatatgca	180
attaatttaa taatttctga tgatggtttt atctgcagta atatgtatat catctattag	240
aatttactta atgaaaaact gaagagaaca aaatttgtaa ccactagcac ttaagtactc	300
ctgattctta acattgtctt taatgaccac aagacaacca acag	344

<210> 342  
 <211> 592  
 <212> DNA  
 <213> Homo sapien

<400> 342	
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caatgtggaa acttcttata cttggttcca ttatgaagtt ggacaattgc tgctatcaca	120
cctggcagggt aaaccaatgc caagagagtg atggaaacca ttggcaagac tttgttgatg	180
accaggattg gaattttata aaaatattgt tgatgggaag ttgctaaagg gtgaattact	240
tccttcagaa gagtgtaaag aaaagtcaga gatgctataa tagcagctat ttaattggc	300
aagtgccact gtggaaagag ttctgtgtg tgctgaagtt ctgaagggca gtcaaattca	360
tcagcatggg ctgtttggtg caaatgcaaa agcacaggtc tttttagcat gctggctctct	420
cccgtgtctt tatgcaaaata atcgtcttct tctaaatttc tcctaggctt cattttccaa	480
agttcttctt ggtttgtgat gtctttcttg ctttccatta attctataaa atagtatggc	540
ttcagccacc cactcttcgc cttagcttga ccgtgagctc cggtgccgc tg	592

<210> 343  
 <211> 382  
 <212> DNA  
 <213> Homo sapien

<400> 343	
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cttgtaactc tcctttctcc tttcttcccc tttctctgcc cgcctttccc atcctgctgt	180
agacttcttg attgtcagtc tgtgtcacat ccagtgattg ttttggtttc tgttcccttt	240
ctgactgccc aaggggctca gaacccagc aatcccttcc tttcactacc ttcttttttg	300
ggggtagttg gaagggactg aaattgtggg gggaaggtag gaggcacatc aataaagagg	360
aaaccaccaa gctgaaaaaa aa	382

<210> 344  
 <211> 536  
 <212> DNA  
 <213> Homo sapien

<400> 344	
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caataggcca cataaacttg gctggatgga acctcacaat aagggtggtca cctcttggtt	120
gtttaggggg atgccaagga taaggccagc tcagttatat gaagagaagc agaacaaaca	180
agtctttcag agaaatggat gcaatcagag tgggatcccc gtcacatcaa ggtcacactc	240
caccttcattg tgcctgaatg gttgccagggt cagaaaaatc cacccttac gaggcggtct	300

tcgaccctat atccccgcc cgcgtccctt totccataaa attcttctta gtagctatta	360
ccttcttatt atttgatcta gaaattgccc tctttttacc cctaccatga gccctacaaa	420
caactaacct gccactaata gttatgtcat ccctcttatt aatcatcatc ctagccctaa	480
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<210> 345  
 <211> 251  
 <212> DNA  
 <213> Homo sapien

<400> 345	
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gcgtgggcca ggaaatcaca tcctacactg cccaggagcc agacacattt atggaacaga	180
aaataacata tcggatttgg agagacactg ccaactggct ggagattaat ccggacactg	240
gtgccatttc c	251

<210> 346  
 <211> 282  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(282)  
 <223> n = A,T,C or G

<400> 346	
cgcgtctctg acactgtgat catgacaggg gttcaaacag aaagtgcctg ggccctcctt	60
ctaagtcttg ttaccataaa aaggaaaaag aaaagatctt ctcaattaca aattctggga	120
aggagagacta tacctggctc ttgccctaag tgagaggtct tccctcccgc accaaaaaat	180
agaaaggctt tctatttcac tgcccaggt agggggaagg agagtaactt tgagtctgtg	240
ggtctcattt cccaaggtgc cttcaatgct catnaaaacc aa	282

<210> 347  
 <211> 201  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(201)  
 <223> n = A,T,C or G

<400> 347	
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tctgagactg actggacca cccagacca gggcaaagat acatgttacc atatcatctt	180
tataaagaat tttttttgt c	201

<210> 348  
 <211> 251  
 <212> DNA  
 <213> Homo sapien

<400> 348	
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agagagaaca gtgccagaat gaaactgacc ctaagtccca ggtgccctg ggcaggcaga	120

aggagacact	cccagcatgg	aggagggttt	atcttttcat	cctaggtcag	gtctacaatg	180
ggggaagggt	ttattataga	actccaaca	gccacctca	ctcctgccac	ccacccgatg	240
gccctgcctc	c					251

&lt;210&gt; 349

&lt;211&gt; 251

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 349

taaaaatcaa	gccatttaat	tgtatctttg	aaggtaaaca	atatatggga	gctggatcac	60
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cagaagggtc	tgaactctac	gtgttaccag	agaacataat	gcaattcatg	cattccactt	180
agcaattttg	taaaatacca	gaaacagacc	ccaagagtc	ttcaagatga	ggaaaattca	240
actcctggtt	t					251

&lt;210&gt; 350

&lt;211&gt; 908

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 350

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aatgcgag						908

&lt;210&gt; 351

&lt;211&gt; 472

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 351

ccagttatatt	gcaagtggta	agagcctatt	taccataaat	aatactaaga	accaactcaa	60
gtcaaacctt	aatgccattg	ttattgtgaa	ttaggattaa	gtagtaattt	tcaaaattca	120
cattaacttg	attttaaaat	cagwtttgyg	agtcattttac	cacaagctaa	atgtgtacac	180
tatgataaaa	acaaccattg	tattcctggt	tttctaaca	gtcctaattt	ctaacactgt	240
atatatcctt	cgacatcaat	gaactttggt	ttcttttact	ccagtaataa	agtaggcaca	300
gatctgtcca	caacaaactt	gccctctcat	gccttgccctc	tcaccatgct	ctgctccagg	360
tcagccccct	tttggcctgt	ttgttttgtc	aaaaaacctaa	tctgcttctt	gcttttcttg	420
gtaatatata	tttaggggaag	atgttgcttt	gccacacac	gaagcaaagt	aa	472

&lt;210&gt; 352

&lt;211&gt; 251

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 352

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tgtggataag	gccagggtcaa	tggctgcaag	catgcagaga	aagagggtaca	tcggagcggtg	120
caggctgcgt	tccgtcctta	cgatgaagac	cacgatgcag	tttccaaaca	ttgccactac	180
atacatggaa	aggaggggga	agccaacca	gaaatgggct	ttctctaate	ctgggataacc	240
aataagcaca	a					251

&lt;210&gt; 353

&lt;211&gt; 436

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 353

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cacattatgg	tattattact	atactgatta	tatttatcat	gtgacttcta	attaraaaat	120
gtatccaaaa	gcaaaacagc	agatatacaa	aattaaagag	acagaagata	gacattaaca	180
gataaggcaa	cttatacatt	gacaatccaa	atccaatata	tttaaacatt	tgggaaatga	240
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tcatgtctga	raaggctctc	ccttcaatgg	ggatgacaaa	ctccaaatgc	cacacaaatg	360
ttaacagaat	actagattca	cactggaacg	ggggtaaaga	agaaattatt	ttctataaaa	420
gggtccttaa	tgtagt					436

&lt;210&gt; 354

&lt;211&gt; 854

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 354

ccttttctag	ttcacaggtt	ttctgcaagg	atgctgggta	gggagtgtct	gcaggaggag	60
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atcagggacc	accctttggg	ttgatatttt	gcttaatctg	catcttttga	gtaagatcat	180
ctggcagtag	aagctgttct	ccagggtacat	ttctctagct	catgtacaaa	aacatcctga	240
aggactttgt	caaggtgcctt	gctaaaagcc	agatgcgttc	ggcacttcct	tgggtctgag	300
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acacgggatg	tcag					854

&lt;210&gt; 355

&lt;211&gt; 676

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 355

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cagggtcaaag	ctgatctttc	tggaaatgtca	ccaaccaagg	gcctatattt	atcaaaaagcc	120
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<210> 356  
 <211> 574  
 <212> DNA  
 <213> Homo sapien

<400> 356						
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caagcttccc	attttagat	ctcagtgcct	atgagtatct	gacacctgtt	cctctcttca	180
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agatacaagc	tctgttacat	gtgatagatc	taacaaaggc	atctaccgaa	gtctggtctg	480
gatagacggc	acaggagcgt	cttaggtcag	cgctgctggg	tggaggacat	tcctgagtc	540
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<210> 357  
 <211> 393  
 <212> DNA  
 <213> Homo sapien

<400> 357						
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aagccacaac	caaracttga	ttttatcaac	aaaaaccct	aaatataaac	ggsaaaaaag	180
atagatataa	ttattccagt	ttttttaaaa	cttaaaarat	attccattgc	cgaattaara	240
araarataag	tgttatatgg	aaagaagggc	attcaagcac	actaaaraaa	cctgaggkaa	300
gcataatctg	tacaaaatta	aactgtcctt	tttggcattt	taacaaattt	gcaacgktct	360
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<210> 358  
 <211> 630  
 <212> DNA  
 <213> Homo sapien

<400> 358						
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ttaatgttta	taggaaaatg	atgagtttat	gacaaaggaa	gtagatagtg	ttttacaaga	120
gcatagagta	gggaagctaa	tccagcacag	ggaggtcaca	gagacatccc	taagggaagt	180
gagtttaaac	tgagagaagc	aagtgcctaa	actgaaggat	gtgttgaaga	agaagggaga	240
gtagaacaat	ttgggcagag	ggaaccttat	agaccctaag	gtgggaaggt	tcaaagaact	300
gaaagagagc	tagaacagct	ggagccgttc	tccggtgtaa	agaggagtca	aagagataag	360
attaaagatg	tgaagattaa	gatcttgggt	gcattcaggg	attggcactt	ctacaagaaa	420
tcaactgaag	gagtaatgtg	acattacttt	tcaactcagg	atggccattc	taactccagg	480
gggtagactg	gactaggtaa	gactggaggc	aggtagacct	cttctaaggc	ctgcgatagt	540
gaaagacaaa	aataagtggg	gaaattcagg	ggatagttaa	aatcagtagg	acttaatgag	600
caagccagag	gttcctccac	aacaaccagt				630

<210> 359  
 <211> 620  
 <212> DNA



&lt;213&gt; Homo sapien

&lt;400&gt; 359

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taattaaaa	atgctactaa	tatagaaaat	ttataatcag	aaaaataaat	attcagggag	120
ctcaccagaa	gaataaagtg	ctctgccagt	tattaaagga	ttactgctgg	tgaattaaat	180
atggcattcc	ccaagggaaa	tagagagatt	cttctggatt	atgttcaata	tttatttcac	240
aggattaact	gttttaggaa	cagatataaa	gcttcgccac	ggaagagatg	gacaaagcac	300
aaagacaaca	tgatacctta	ggaagcaaca	ctaccctttc	aggcataaaa	tttggagaaa	360
tgcaacatta	tgcttcatga	ataatatgta	gaaagaaggt	ctgatgaaaa	tgacatcctt	420
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aatgtcattg	acttatcaaa	tactatcttg	gcataatacc	tatgaaggca	aaactaaaca	540
aacaaaaagc	tcacaccaa	caaaaccatc	aacttatttt	gtattctata	acatacgaga	600
ctgtaaagat	gtgacagtgt					620

&lt;210&gt; 360

&lt;211&gt; 431

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 360

aaaaaaaa	agccagaaca	acatgtgata	gataatatga	ttggtgcac	acttcagac	60
tgatgaatga	tgaacgtgat	ggactattgt	atggagcaca	tcttcagcaa	gagggggaaa	120
tactcatcat	ttttggccag	cagttgtttg	atcaccaaac	atcatgccag	aatactcagc	180
aaaccttctt	agctcttgag	aagtcaaagt	ccgggggaat	ttattcctgg	caattttaat	240
tggactcctt	atgtgagagc	agcggctacc	cagctggggt	ggtggagcga	accggtcact	300
agtggacatg	cagtggcaga	gctcctggta	accacctaga	ggaatacaca	ggcacatgtg	360
tgatgccaa	cgtagacac	gtagactca	aatttgtctt	gtttttgtct	ttcgggtgtg	420
agattcttag	t					431

&lt;210&gt; 361

&lt;211&gt; 351

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 361

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ctgccactct	gtctccagc	tctgacagct	cctcatctgt	ggtcctgttg	t	351

&lt;210&gt; 362

&lt;211&gt; 463

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 362

acttcatcag	gccataatgg	gtgcctcccg	tgagaatcca	agcacctttg	gactgcgcga	60
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ccccggtcac	agaaatgacc	aggttgggtg	ttttcagggtg	ccagtgtctg	gtcagcagct	180
cgtaaaggat	ttccgcgtcc	gtgtcgcagg	acagacgtat	atacttccct	ttcttcccca	240
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agttccattt	ctcacttttg	ttgatctggg	tgcttcccat	gtgtcggctc	tgggcatagc	360
cacacttgca	cacattctcc	ctgataagca	cgatggtgtg	gacaggaagg	aaggatttca	420
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<210> 363  
 <211> 653  
 <212> DNA  
 <213> Homo sapien  
 <220>  
 <221> misc\_feature  
 <222> (1)...(653)  
 <223> n = A,T,C or G

<400> 363  
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 ctcttgngga ttctgggtga catcttcatg aatggcaacc gtgccagwga ggctgtcctc 120  
 tgggaggcac tacgcaagat gggactgctg cctgggggtga gacatcctct ccttggagat 180  
 ctaacgaaac ttctcaccta tgagttgtaa agcagaaata cctgnactac agacgagtgc 240  
 ccaacagcaa cccccggaa gtatgagttc ctctrgggcc tccgttccta ccatgagasc 300  
 tagcaagatg naagtgttga gantcattgc agaggttcag aaaagagacc cntcgtgact 360  
 ggtctgcaca gttcatggag gctgcagatg aggccttggg tgcctctggat gctgctgcag 420  
 ctgaggccga agcccgggct gaagcaagaa cccgcattgg aattggagat gaggctgtgt 480  
 ntgggccctg gactgtggat gacattgagt ttgagctgct gacctgggat gaggaaggag 540  
 attttgagga tccttgggtcc agaattccat ttaccttctg ggccagatac caccagaatg 600  
 cccgctccag attccctcag acctttgccg gtcccattat tggctcstggt ggt 653

<210> 364  
 <211> 401  
 <212> DNA  
 <213> Homo sapien

<400> 364  
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 aaaacaaggt ggatagatct agaattgtaa cattttaaga aaaccatagc atttgacaga 180  
 tgagaaagct caattataga tgcaaagtta taactaaact actatagtag taaagaaata 240  
 catttcacac ccttcataata aattcactat cttggcttga ggcactccat aaaatgtatc 300  
 acgtgcatag taaatcttta tatttgctat ggcgttgac tagaggactt ggactgcaac 360  
 aagtggatgc gcggaaaatg aaatcttctt caatagccca g 401

<210> 365  
 <211> 356  
 <212> DNA  
 <213> Homo sapien

<400> 365  
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 atgtttcagt gctagagcgt aggaatagac cctggcgctc actgtgagat gttcttcagc 120  
 taccagagca tcaagtctct gcagcaggtc attcttgggt aaagaaatga cttccacaaa 180  
 ctctccatcc cctggctttg gcttcggcct tgcgttttcg gcatcatctc cgttaaatggt 240  
 gactgtcacg atgtgtatag tacagtttga caagcctggg tccatacaga ccgctggaga 300  
 acattcggca atgtcccctt tgtagccagt ttcttcttcg agctcccga gagcag 356

<210> 366  
 <211> 1851  
 <212> DNA  
 <213> Homo sapien

<400> 366  
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tcacttcctt	taagcctttg	tgactcttcc	tctgatgtca	gctttaagtc	ttgttctgga	180
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caaattacat	gatgatgact	agaaacagca	tactctctgg	ccgtctttcc	agatcttgag	300
aagatacatc	aacattttgc	tcaagtagag	ggctgactat	acttgctgat	ccacaacata	360
cagcaagtat	gagagcagtt	cttccatatc	tatccagcgc	atttaaattc	gcttttttct	420
tgattaaaaa	tttcaccact	tgctgttttt	gctcatgtat	accaagtagc	agtgggtgga	480
ggccatgctt	gttttttgat	tcgatatcag	caccgtataa	gagcagtgtc	ttggccatta	540
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gcacgagttt	tactacttct	gaattcccat	tggcagaggc	cagatgtaga	gcagtcctct	780
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ccagtgcag	agaagccaca	ctgaagctct	gtcctcagcc	atcagcgcca	cggacaggar	1500
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gtccttgaga	aacaccccag	ctcttccggt	ctaacacagg	caagtcaata	aatgtgataa	1620
tcacataaaa	agaattaaaa	gcaaagtcac	ataagcatct	caacagacac	agaaaaggca	1680
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cttttcccca	tttagtatta	tgttggctgt	gggcttgtca	taggtgggtt	ttattacttt	1800
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<210> 367  
 <211> 668  
 <212> DNA  
 <213> Homo sapien

<400> 367						
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accrtataag	agcagtgcct	tggccattaa	tttatctttc	attttagaca	gcrtagtgya	180
gagtggtatt	tccatactca	tctggaatat	ttggatcagt	gccatgttcc	agcaacatta	240
acgcacattc	atcttccctg	cattgtacgg	cctgtcagta	ttagacccaa	aaacaaatta	300
catatcttag	gaattcaaaa	taacattcca	cagctttcac	caactagtta	tatttaaagg	360
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gcagtcctat	gagagtgaga	agacttttta	ggaaattgta	gtgcactagc	tacagccata	600
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aaaaaaaa						668

<210> 368  
 <211> 1512  
 <212> DNA  
 <213> Homo sapien

<400> 368						
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ttcaaacaga	ttggaaaccc	ggagttacct	gctagttggt	gaaactggtt	ggtagacgcg	180

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gccttcatgg	agcccaggta	ccacgtccgt	ggagaagatc	tggacaagct	ccacagagct	660
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gaagtagtaa	aactcstgct	ggacagacga	tgtcaactta	atgtccttga	caacaaaaag	840
aggacagctc	tgayaaaggc	cgtacaatgc	caggaagatg	aatgtgcgtt	aatgttgctg	900
gaacatggca	ctgatccaaa	tattccagat	gagtatggaa	ataccactct	rcactaygct	960
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tcaaaaaaca	aggtatagat	ctactaattt	tatcttcaaa	atactgaaat	gcattcattt	1080
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actccaagaa	aagttaaaca	tgtttcagt	aatagagatc	ctgctccttt	ggcaagttcc	1440
taaaaaacag	taatagatac	gaggtgatgc	gcctgtcagt	ggcaagggtt	aagatatttc	1500
tgatctcgtg	cc					1512

&lt;210&gt; 369

&lt;211&gt; 1853

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 369

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<210> 370  
 <211> 2184  
 <212> DNA  
 <213> Homo sapien

<400> 370						
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agacttaaaag	ctgacatcag	aggaagagtc	acaaaggctt	aaaggaagtg	aaaacagcca	1740
gccagaggca	tggaaacttt	taaattttaa	cttttggttt	aatgtttttt	ttttttgcct	1800
taataatatt	agatagtccc	aaatgaaatw	acctatgaga	ctaggctttg	agaatcaata	1860
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cggtgaaacc	ccatctctac	taaaaatata	aaaacttagc	tgggtgtggt	ggcgggtgcc	2040
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ctcaaaaaaa	aaaaaaaaaa	aaaa				2184

<210> 371  
 <211> 1855  
 <212> DNA  
 <213> Homo sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(1855)  
 <223> n = A,T,C or G

## &lt;400&gt; 371

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gccgcccc	cataaccg	agactggc	gtaacggct	gcaggcgc	gccgcacgc	180
cgtaacgg	tggtgccct	gtaacggct	gcacgtgc	gctgcacgc	cgtaacgg	240
ttggctgg	tgtagccg	tggttggc	ttgcattyt	tgtkggctk	ggcgttgky	300
tcttggatt	acgttctc	cttggatk	cgtttctcc	ttggatkga	gtttcytyt	360
tcgcgttct	ttgctggac	tgaccttt	tctgctggg	ttggcattc	tttggggtg	420
gctgggtgt	ttctccggg	gggkkgccc	ttctgggg	gggcgtggg	cgccccagg	480
gggcgtggg	ttccccggg	tgggtgtgg	ttttctggg	gtggggtgg	ctgtgctgg	540
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gtaacntgt	agttggtga	actggttgg	agacgcgat	tgctggtac	actgtttct	660
ctggtctgt	aaagcagat	gtggctgag	ttgattcaat	gccggctgt	tcttctgtg	720
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cagtttttt	tttttaaat	cacttctgt	aaatacttt	gttgaaaac	ctgaattgt	1620
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tgtaagatg	caaaatttg	cctgaaatg	gttttacat	aaaactcaa	gaaaagtaa	1740
acatgtttc	gtgaatag	atcctgtcc	tttggaagt	tcttaaaaa	cagtaatag	1800
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## &lt;210&gt; 372

## &lt;211&gt; 1059

## &lt;212&gt; DNA

## &lt;213&gt; Homo sapien

## &lt;400&gt; 372

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gcgcttgrg	agactmcga	gacagygct	tcatggagc	caggtacc	gtccgtggg	180
aagatctga	caagctcc	agagctgcc	tgggtgggt	aagtcccc	aaaggatct	240
atcgctatg	tcagggac	tgaygtga	aagarggac	agcaaaag	gactgctct	300
catctggc	ctgccaatg	gaattcaga	gtagtaaac	tcstgctga	cagacgatg	360
caacttaat	tccttgaca	caaaaagag	acagctctg	yaaaggcgt	acaatgcc	420
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tatggaaat	ccactctr	ctaygctrt	tayaatga	ataaattat	ggccaaagc	540
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ctttatttt	aatattgta	ttttcaaga	agcattag	ggtacagtt	tttttttt	780
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tatttttca	tttttccct	ctaggattt	tttccccta	tgaatgta	atggcaaat	900
ttggccctg	ataggtttt	catgaaaat	ccaagaaa	ttaaacatg	ttcagtga	960
agagatcct	ctcctttgg	aagttocta	aaaacagta	tagatacga	gtgatgcgc	1020
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<210> 373  
 <211> 1155  
 <212> DNA  
 <213> Homo sapien

<400> 373  
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 agcaacgttg gcacttcttg agaccacgac gactctgcta tgaagacact caggagcaag 180  
 atgggcaagt ggtgccgcca ctgcttcccc tgctgcaggg ggagtggcaa gagcaacgtg 240  
 ggcgcttctg gagaccacga cgactctgct atgaagacac tcaggaacaa gatgggcaag 300  
 tgggtgctgcc actgcttccc ctgctgcagg gggagcggca agagcaaggt gggcgcttgg 360  
 ggagactacg atgacagtgc cttcatggag cccaggtagc acgtccgtgg agaagatctg 420  
 gacaagctcc acagagctgc ctggtggggt aaagtcccca gaaaggatct catcgtcatg 480  
 ctcagggaca ctgacgtgaa caagaaggac aagcaaaaaga ggactgctct acatctggcc 540  
 tctgccaatg ggaattcaga agtagtaaaa ctctgctgg acagacgatg tcaacttaat 600  
 gtcttgaca acaaaaagag gacagctctg ataaaggccg tacaatgcca ggaagatgaa 660  
 tgtgcgttaa tgttgctgga acatggcact gatccaaata ttccagatga gtatggaaat 720  
 accactctgc actacgctat ctataatgaa gataaattaa tggccaaagc actgctctta 780  
 tatggtgctg atatcgaatc aaaaaacaag catggcctca caccactgtt acttggtgta 840  
 catgagcaaa aacagcaagt cgtgaaattt ttaatcaaga aaaaagcgaa tttaaatgca 900  
 ctggatagat atggaaggac tgctctcata cttgctgtat gttgtggatc agcaagtata 960  
 gtcagccttc tacttgagca aaatattgat gtatcttctc aagatctatc tggacagacg 1020  
 gccagagagt atgctgtttc tagtcatcat catgtaattt gccagttact ttctgactac 1080  
 aaagaaaaac agatgctaaa aatctcttct gaaaacagca atccagaaaa tgtctcaaga 1140  
 accagaaata aataa 1155

<210> 374  
 <211> 2000  
 <212> DNA  
 <213> Homo sapien

<400> 374  
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 agcaacgttg gcacttcttg agaccacgac gactctgcta tgaagacact caggagcaag 180  
 atgggcaagt ggtgccgcca ctgcttcccc tgctgcaggg ggagtggcaa gagcaacgtg 240  
 ggcgcttctg gagaccacga cgactctgct atgaagacac tcaggaacaa gatgggcaag 300  
 tgggtgctgcc actgcttccc ctgctgcagg gggagcggca agagcaaggt gggcgcttgg 360  
 ggagactacg atgacagtgc cttcatggag cccaggtagc acgtccgtgg agaagatctg 420  
 gacaagctcc acagagctgc ctggtggggt aaagtcccca gaaaggatct catcgtcatg 480  
 ctcagggaca ctgacgtgaa caagaaggac aagcaaaaaga ggactgctct acatctggcc 540  
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 gtcttgaca acaaaaagag gacagctctg ataaaggccg tacaatgcca ggaagatgaa 660  
 tgtgcgttaa tgttgctgga acatggcact gatccaaata ttccagatga gtatggaaat 720  
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 aatggtgata atggattaat tcctcaaagg aagagcagaa cacctgaaaa tcagcaattt 1380  
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 aaacagatgc caaaatactc ttctgaaaac agcaaccag aacaagactt aaagctgaca 1500

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gccatgctaa	gactggagct	agacacaatg	aaacatcaga	gccagctaaa	aaaaaaaaaa	1980
aaaaaaaaaa	aaaaaaaaaa					2000

&lt;210&gt; 375

&lt;211&gt; 2040

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 375

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gaaaaagaca	tcttgcatga	aaatagtacg	ttgcgggaag	aaattgccat	gctaagactg	1980
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&lt;210&gt; 376

&lt;211&gt; 329

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 376

Met Asp Ile Val Val Ser Gly Ser His Pro Leu Trp Val Asp Ser Phe



```

1           5           10           15
Leu His Leu Ala Gly Ser Asp Leu Leu Ser Arg Ser Leu Met Ala Glu
20           25           30
Glu Tyr Thr Ile Val His Ala Ser Phe Ile Ser Cys Ile Ser Ser Ser
35           40           45
Leu Asp Gly Gln Gly Glu Arg Gln Glu Gln Arg Gly His Phe Trp Arg
50           55           60
Pro Gln Arg Leu Leu Cys Glu Asp Ala Trp Glu Gln Glu Val Gln Val
65           70           75           80
Val Leu Pro Leu Leu Pro Leu Leu Gln Gly Ser Gly Lys Ser Asn Val
85           90           95
Val Ala Trp Gly Asp Tyr Asp Asp Ser Ala Phe Met Asp Pro Arg Tyr
100          105          110
His Val His Gly Glu Asp Leu Asp Lys Leu His Arg Ala Ala Trp Trp
115          120          125
Gly Lys Val Pro Arg Lys Asp Leu Ile Val Met Leu Arg Asp Thr Asp
130          135          140
Val Asn Lys Arg Asp Lys Gln Lys Arg Thr Ala Leu His Leu Ala Ser
145          150          155          160
Ala Asn Gly Asn Ser Glu Val Val Lys Leu Val Leu Asp Arg Arg Cys
165          170          175
Gln Leu Asn Val Leu Asp Asn Lys Lys Arg Thr Ala Leu Thr Lys Ala
180          185          190
Val Gln Cys Gln Glu Asp Glu Cys Ala Leu Met Leu Leu Glu His Gly
195          200          205
Thr Asp Pro Asn Ile Pro Asp Glu Tyr Gly Asn Thr Thr Leu His Tyr
210          215          220
Ala Val Tyr Asn Glu Asp Lys Leu Met Ala Lys Ala Leu Leu Leu Tyr
225          230          235          240
Gly Ala Asp Ile Glu Ser Lys Asn Lys His Gly Leu Thr Pro Leu Leu
245          250          255
Leu Gly Ile His Glu Gln Lys Gln Gln Val Val Lys Phe Leu Ile Lys
260          265          270
Lys Lys Ala Asn Leu Asn Ala Leu Asp Arg Tyr Gly Arg Thr Ala Leu
275          280          285
Ile Leu Ala Val Cys Cys Gly Ser Ala Ser Ile Val Ser Pro Leu Leu
290          295          300
Glu Gln Asn Val Asp Val Ser Ser Gln Asp Leu Glu Arg Arg Pro Glu
305          310          315          320
Ser Met Leu Phe Leu Val Ile Ile Met
325

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<210> 377  
 <211> 148  
 <212> PRT  
 <213> Homo sapien

<220>  
 <221> VARIANT  
 <222> (1)...(148)  
 <223> Xaa = Any Amino Acid

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Trp Thr Ser Ser Thr Glu Leu Pro Trp Trp Gly Lys Val Pro Arg Lys
20           25           30
Asp Leu Ile Val Met Leu Arg Asp Thr Asp Val Asn Lys Xaa Asp Lys

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35 40 45  
 Gln Lys Arg Thr Ala Leu His Leu Ala Ser Ala Asn Gly Asn Ser Glu  
 50 55 60  
 Val Val Lys Leu Xaa Leu Asp Arg Arg Cys Gln Leu Asn Val Leu Asp  
 65 70 75 80  
 Asn Lys Lys Arg Thr Ala Leu Xaa Lys Ala Val Gln Cys Gln Glu Asp  
 85 90 95  
 Glu Cys Ala Leu Met Leu Leu Glu His Gly Thr Asp Pro Asn Ile Pro  
 100 105 110  
 Asp Glu Tyr Gly Asn Thr Thr Leu His Tyr Ala Xaa Tyr Asn Glu Asp  
 115 120 125  
 Lys Leu Met Ala Lys Ala Leu Leu Leu Tyr Gly Ala Asp Ile Glu Ser  
 130 135 140  
 Lys Asn Lys Val  
 145

<210> 378  
 <211> 1719  
 <212> PRT  
 <213> Homo sapien

<400> 378  
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 Pro Cys Cys Arg Glu Ser Gly Lys Ser Asn Val Gly Thr Ser Gly Asp  
 35 40 45  
 His Asp Asp Ser Ala Met Lys Thr Leu Arg Ser Lys Met Gly Lys Trp  
 50 55 60  
 Cys Arg His Cys Phe Pro Cys Cys Arg Gly Ser Gly Lys Ser Asn Val  
 65 70 75 80  
 Gly Ala Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr Leu Arg Asn  
 85 90 95  
 Lys Met Gly Lys Trp Cys Cys His Cys Phe Pro Cys Cys Arg Gly Ser  
 100 105 110  
 Gly Lys Ser Lys Val Gly Ala Trp Gly Asp Tyr Asp Asp Ser Ala Phe  
 115 120 125  
 Met Glu Pro Arg Tyr His Val Arg Gly Glu Asp Leu Asp Lys Leu His  
 130 135 140  
 Arg Ala Ala Trp Trp Gly Lys Val Pro Arg Lys Asp Leu Ile Val Met  
 145 150 155 160  
 Leu Arg Asp Thr Asp Val Asn Lys Lys Asp Lys Gln Lys Arg Thr Ala  
 165 170 175  
 Leu His Leu Ala Ser Ala Asn Gly Asn Ser Glu Val Val Lys Leu Leu  
 180 185 190  
 Leu Asp Arg Arg Cys Gln Leu Asn Val Leu Asp Asn Lys Lys Arg Thr  
 195 200 205  
 Ala Leu Ile Lys Ala Val Gln Cys Gln Glu Asp Glu Cys Ala Leu Met  
 210 215 220  
 Leu Leu Glu His Gly Thr Asp Pro Asn Ile Pro Asp Glu Tyr Gly Asn  
 225 230 235 240  
 Thr Thr Leu His Tyr Ala Ile Tyr Asn Glu Asp Lys Leu Met Ala Lys  
 245 250 255  
 Ala Leu Leu Leu Tyr Gly Ala Asp Ile Glu Ser Lys Asn Lys His Gly  
 260 265 270  
 Leu Thr Pro Leu Leu Leu Gly Val His Glu Gln Lys Gln Gln Val Val  
 275 280 285

Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu Asn Ala Leu Asp Arg Tyr  
 290 295 300  
 Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly Ser Ala Ser Ile  
 305 310 315 320  
 Val Ser Leu Leu Leu Glu Gln Asn Ile Asp Val Ser Ser Gln Asp Leu  
 325 330 335  
 Ser Gly Gln Thr Ala Arg Glu Tyr Ala Val Ser Ser His His His Val  
 340 345 350  
 Ile Cys Gln Leu Leu Ser Asp Tyr Lys Glu Lys Gln Met Leu Lys Ile  
 355 360 365  
 Ser Ser Glu Asn Ser Asn Pro Glu Asn Val Ser Arg Thr Arg Asn Lys  
 370 375 380  
 Pro Arg Thr His Met Val Val Glu Val Asp Ser Met Pro Ala Ala Ser  
 385 390 395 400  
 Ser Val Lys Lys Pro Phe Gly Leu Arg Ser Lys Met Gly Lys Trp Cys  
 405 410 415  
 Cys Arg Cys Phe Pro Cys Cys Arg Glu Ser Gly Lys Ser Asn Val Gly  
 420 425 430  
 Thr Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr Leu Arg Ser Lys  
 435 440 445  
 Met Gly Lys Trp Cys Arg His Cys Phe Pro Cys Cys Arg Gly Ser Gly  
 450 455 460  
 Lys Ser Asn Val Gly Ala Ser Gly Asp His Asp Asp Ser Ala Met Lys  
 465 470 475 480  
 Thr Leu Arg Asn Lys Met Gly Lys Trp Cys Cys His Cys Phe Pro Cys  
 485 490 495  
 Cys Arg Gly Ser Gly Lys Ser Lys Val Gly Ala Trp Gly Asp Tyr Asp  
 500 505 510  
 Asp Ser Ala Phe Met Glu Pro Arg Tyr His Val Arg Gly Glu Asp Leu  
 515 520 525  
 Asp Lys Leu His Arg Ala Ala Trp Trp Gly Lys Val Pro Arg Lys Asp  
 530 535 540  
 Leu Ile Val Met Leu Arg Asp Thr Asp Val Asn Lys Lys Asp Lys Gln  
 545 550 555 560  
 Lys Arg Thr Ala Leu His Leu Ala Ser Ala Asn Gly Asn Ser Glu Val  
 565 570 575  
 Val Lys Leu Leu Leu Asp Arg Arg Cys Gln Leu Asn Val Leu Asp Asn  
 580 585 590  
 Lys Lys Arg Thr Ala Leu Ile Lys Ala Val Gln Cys Gln Glu Asp Glu  
 595 600 605  
 Cys Ala Leu Met Leu Leu Glu His Gly Thr Asp Pro Asn Ile Pro Asp  
 610 615 620  
 Glu Tyr Gly Asn Thr Thr Leu His Tyr Ala Ile Tyr Asn Glu Asp Lys  
 625 630 635 640  
 Leu Met Ala Lys Ala Leu Leu Leu Tyr Gly Ala Asp Ile Glu Ser Lys  
 645 650 655  
 Asn Lys His Gly Leu Thr Pro Leu Leu Gly Val His Glu Gln Lys  
 660 665 670  
 Gln Gln Val Val Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu Asn Ala  
 675 680 685  
 Leu Asp Arg Tyr Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly  
 690 695 700  
 Ser Ala Ser Ile Val Ser Leu Leu Leu Glu Gln Asn Ile Asp Val Ser  
 705 710 715 720  
 Ser Gln Asp Leu Ser Gly Gln Thr Ala Arg Glu Tyr Ala Val Ser Ser  
 725 730 735  
 His His His Val Ile Cys Gln Leu Leu Ser Asp Tyr Lys Glu Lys Gln  
 740 745 750

Met Leu Lys Ile Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp Leu Lys  
 755 760 765  
 Leu Thr Ser Glu Glu Glu Ser Gln Arg Phe Lys Gly Ser Glu Asn Ser  
 770 775 780  
 Gln Pro Glu Lys Met Ser Gln Glu Pro Glu Ile Asn Lys Asp Gly Asp  
 785 790 795 800  
 Arg Glu Val Glu Glu Glu Met Lys Lys His Glu Ser Asn Asn Val Gly  
 805 810 815  
 Leu Leu Glu Asn Leu Thr Asn Gly Val Thr Ala Gly Asn Gly Asp Asn  
 820 825 830  
 Gly Leu Ile Pro Gln Arg Lys Ser Arg Thr Pro Glu Asn Gln Gln Phe  
 835 840 845  
 Pro Asp Asn Glu Ser Glu Glu Tyr His Arg Ile Cys Glu Leu Val Ser  
 850 855 860  
 Asp Tyr Lys Glu Lys Gln Met Pro Lys Tyr Ser Ser Glu Asn Ser Asn  
 865 870 875 880  
 Pro Glu Gln Asp Leu Lys Leu Thr Ser Glu Glu Glu Ser Gln Arg Leu  
 885 890 895  
 Glu Gly Ser Glu Asn Gly Gln Pro Glu Leu Glu Asn Phe Met Ala Ile  
 900 905 910  
 Glu Glu Met Lys Lys His Gly Ser Thr His Val Gly Phe Pro Glu Asn  
 915 920 925  
 Leu Thr Asn Gly Ala Thr Ala Gly Asn Gly Asp Asp Gly Leu Ile Pro  
 930 935 940  
 Pro Arg Lys Ser Arg Thr Pro Glu Ser Gln Gln Phe Pro Asp Thr Glu  
 945 950 955 960  
 Asn Glu Glu Tyr His Ser Asp Glu Gln Asn Asp Thr Gln Lys Gln Phe  
 965 970 975  
 Cys Glu Glu Gln Asn Thr Gly Ile Leu His Asp Glu Ile Leu Ile His  
 980 985 990  
 Glu Glu Lys Gln Ile Glu Val Val Glu Lys Met Asn Ser Glu Leu Ser  
 995 1000 1005  
 Leu Ser Cys Lys Lys Glu Lys Asp Ile Leu His Glu Asn Ser Thr Leu  
 1010 1015 1020  
 Arg Glu Glu Ile Ala Met Leu Arg Leu Glu Leu Asp Thr Met Lys His  
 1025 1030 1035 1040  
 Gln Ser Gln Leu Pro Arg Thr His Met Val Val Glu Val Asp Ser Met  
 1045 1050 1055  
 Pro Ala Ala Ser Ser Val Lys Lys Pro Phe Gly Leu Arg Ser Lys Met  
 1060 1065 1070  
 Gly Lys Trp Cys Cys Arg Cys Phe Pro Cys Cys Arg Glu Ser Gly Lys  
 1075 1080 1085  
 Ser Asn Val Gly Thr Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr  
 1090 1095 1100  
 Leu Arg Ser Lys Met Gly Lys Trp Cys Arg His Cys Phe Pro Cys Cys  
 1105 1110 1115 1120  
 Arg Gly Ser Gly Lys Ser Asn Val Gly Ala Ser Gly Asp His Asp Asp  
 1125 1130 1135  
 Ser Ala Met Lys Thr Leu Arg Asn Lys Met Gly Lys Trp Cys Cys His  
 1140 1145 1150  
 Cys Phe Pro Cys Cys Arg Gly Ser Gly Lys Ser Lys Val Gly Ala Trp  
 1155 1160 1165  
 Gly Asp Tyr Asp Asp Ser Ala Phe Met Glu Pro Arg Tyr His Val Arg  
 1170 1175 1180  
 Gly Glu Asp Leu Asp Lys Leu His Arg Ala Ala Trp Trp Gly Lys Val  
 1185 1190 1195 1200  
 Pro Arg Lys Asp Leu Ile Val Met Leu Arg Asp Thr Asp Val Asn Lys  
 1205 1210 1215

Lys Asp Lys Gln Lys Arg Thr Ala Leu His Leu Ala Ser Ala Asn Gly  
 1220 1225 1230  
 Asn Ser Glu Val Val Lys Leu Leu Asp Arg Arg Cys Gln Leu Asn  
 1235 1240 1245  
 Val Leu Asp Asn Lys Lys Arg Thr Ala Leu Ile Lys Ala Val Gln Cys  
 1250 1255 1260  
 Gln Glu Asp Glu Cys Ala Leu Met Leu Leu Glu His Gly Thr Asp Pro  
 1265 1270 1275 1280  
 Asn Ile Pro Asp Glu Tyr Gly Asn Thr Thr Leu His Tyr Ala Ile Tyr  
 1285 1290 1295  
 Asn Glu Asp Lys Leu Met Ala Lys Ala Leu Leu Leu Tyr Gly Ala Asp  
 1300 1305 1310  
 Ile Glu Ser Lys Asn Lys His Gly Leu Thr Pro Leu Leu Leu Gly Val  
 1315 1320 1325  
 His Glu Gln Lys Gln Gln Val Val Lys Phe Leu Ile Lys Lys Lys Ala  
 1330 1335 1340  
 Asn Leu Asn Ala Leu Asp Arg Tyr Gly Arg Thr Ala Leu Ile Leu Ala  
 1345 1350 1355 1360  
 Val Cys Cys Gly Ser Ala Ser Ile Val Ser Leu Leu Leu Glu Gln Asn  
 1365 1370 1375  
 Ile Asp Val Ser Ser Gln Asp Leu Ser Gly Gln Thr Ala Arg Glu Tyr  
 1380 1385 1390  
 Ala Val Ser Ser His His His Val Ile Cys Gln Leu Leu Ser Asp Tyr  
 1395 1400 1405  
 Lys Glu Lys Gln Met Leu Lys Ile Ser Ser Glu Asn Ser Asn Pro Glu  
 1410 1415 1420  
 Gln Asp Leu Lys Leu Thr Ser Glu Glu Glu Ser Gln Arg Phe Lys Gly  
 1425 1430 1435 1440  
 Ser Glu Asn Ser Gln Pro Glu Lys Met Ser Gln Glu Pro Glu Ile Asn  
 1445 1450 1455  
 Lys Asp Gly Asp Arg Glu Val Glu Glu Glu Met Lys Lys His Glu Ser  
 1460 1465 1470  
 Asn Asn Val Gly Leu Leu Glu Asn Leu Thr Asn Gly Val Thr Ala Gly  
 1475 1480 1485  
 Asn Gly Asp Asn Gly Leu Ile Pro Gln Arg Lys Ser Arg Thr Pro Glu  
 1490 1495 1500  
 Asn Gln Gln Phe Pro Asp Asn Glu Ser Glu Glu Tyr His Arg Ile Cys  
 1505 1510 1515 1520  
 Glu Leu Val Ser Asp Tyr Lys Glu Lys Gln Met Pro Lys Tyr Ser Ser  
 1525 1530 1535  
 Glu Asn Ser Asn Pro Glu Gln Asp Leu Lys Leu Thr Ser Glu Glu Glu  
 1540 1545 1550  
 Ser Gln Arg Leu Glu Gly Ser Glu Asn Gly Gln Pro Glu Lys Arg Ser  
 1555 1560 1565  
 Gln Glu Pro Glu Ile Asn Lys Asp Gly Asp Arg Glu Leu Glu Asn Phe  
 1570 1575 1580  
 Met Ala Ile Glu Glu Met Lys Lys His Gly Ser Thr His Val Gly Phe  
 1585 1590 1595 1600  
 Pro Glu Asn Leu Thr Asn Gly Ala Thr Ala Gly Asn Gly Asp Asp Gly  
 1605 1610 1615  
 Leu Ile Pro Pro Arg Lys Ser Arg Thr Pro Glu Ser Gln Gln Phe Pro  
 1620 1625 1630  
 Asp Thr Glu Asn Glu Glu Tyr His Ser Asp Glu Gln Asn Asp Thr Gln  
 1635 1640 1645  
 Lys Gln Phe Cys Glu Glu Gln Asn Thr Gly Ile Leu His Asp Glu Ile  
 1650 1655 1660  
 Leu Ile His Glu Glu Lys Gln Ile Glu Val Val Glu Lys Met Asn Ser  
 1665 1670 1675 1680

Glu Leu Ser Leu Ser Cys Lys Lys Glu Lys Asp Ile Leu His Glu Asn  
 1685 1690 1695  
 Ser Thr Leu Arg Glu Glu Ile Ala Met Leu Arg Leu Glu Leu Asp Thr  
 1700 1705 1710  
 Met Lys His Gln Ser Gln Leu  
 1715

<210> 379  
 <211> 656  
 <212> PRT  
 <213> Homo sapien

<400> 379  
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 20 25 30  
 Pro Cys Cys Arg Glu Ser Gly Lys Ser Asn Val Gly Thr Ser Gly Asp  
 35 40 45  
 His Asp Asp Ser Ala Met Lys Thr Leu Arg Ser Lys Met Gly Lys Trp  
 50 55 60  
 Cys Arg His Cys Phe Pro Cys Cys Arg Gly Ser Gly Lys Ser Asn Val  
 65 70 75 80  
 Gly Ala Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr Leu Arg Asn  
 85 90 95  
 Lys Met Gly Lys Trp Cys Cys His Cys Phe Pro Cys Cys Arg Gly Ser  
 100 105 110  
 Gly Lys Ser Lys Val Gly Ala Trp Gly Asp Tyr Asp Asp Ser Ala Phe  
 115 120 125  
 Met Glu Pro Arg Tyr His Val Arg Gly Glu Asp Leu Asp Lys Leu His  
 130 135 140  
 Arg Ala Ala Trp Trp Gly Lys Val Pro Arg Lys Asp Leu Ile Val Met  
 145 150 155 160  
 Leu Arg Asp Thr Asp Val Asn Lys Lys Asp Lys Gln Lys Arg Thr Ala  
 165 170 175  
 Leu His Leu Ala Ser Ala Asn Gly Asn Ser Glu Val Val Lys Leu Leu  
 180 185 190  
 Leu Asp Arg Arg Cys Gln Leu Asn Val Leu Asp Asn Lys Lys Arg Thr  
 195 200 205  
 Ala Leu Ile Lys Ala Val Gln Cys Gln Glu Asp Glu Cys Ala Leu Met  
 210 215 220  
 Leu Leu Glu His Gly Thr Asp Pro Asn Ile Pro Asp Glu Tyr Gly Asn  
 225 230 235 240  
 Thr Thr Leu His Tyr Ala Ile Tyr Asn Glu Asp Lys Leu Met Ala Lys  
 245 250 255  
 Ala Leu Leu Leu Tyr Gly Ala Asp Ile Glu Ser Lys Asn Lys His Gly  
 260 265 270  
 Leu Thr Pro Leu Leu Leu Gly Val His Glu Gln Lys Gln Gln Val Val  
 275 280 285  
 Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu Asn Ala Leu Asp Arg Tyr  
 290 295 300  
 Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly Ser Ala Ser Ile  
 305 310 315 320  
 Val Ser Leu Leu Leu Glu Gln Asn Ile Asp Val Ser Ser Gln Asp Leu  
 325 330 335  
 Ser Gly Gln Thr Ala Arg Glu Tyr Ala Val Ser Ser His His His Val  
 340 345 350  
 Ile Cys Gln Leu Leu Ser Asp Tyr Lys Glu Lys Gln Met Leu Lys Ile

355	360	365
Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp Leu Lys Leu Thr Ser Glu		
370	375	380
Glu Glu Ser Gln Arg Phe Lys Gly Ser Glu Asn Ser Gln Pro Glu Lys		
385	390	395
Met Ser Gln Glu Pro Glu Ile Asn Lys Asp Gly Asp Arg Glu Val Glu		
405	410	415
Glu Glu Met Lys Lys His Glu Ser Asn Asn Val Gly Leu Leu Glu Asn		
420	425	430
Leu Thr Asn Gly Val Thr Ala Gly Asn Gly Asp Asn Gly Leu Ile Pro		
435	440	445
Gln Arg Lys Ser Arg Thr Pro Glu Asn Gln Gln Phe Pro Asp Asn Glu		
450	455	460
Ser Glu Glu Tyr His Arg Ile Cys Glu Leu Val Ser Asp Tyr Lys Glu		
465	470	475
Lys Gln Met Pro Lys Tyr Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp		
485	490	495
Leu Lys Leu Thr Ser Glu Glu Glu Ser Gln Arg Leu Glu Gly Ser Glu		
500	505	510
Asn Gly Gln Pro Glu Leu Glu Asn Phe Met Ala Ile Glu Glu Met Lys		
515	520	525
Lys His Gly Ser Thr His Val Gly Phe Pro Glu Asn Leu Thr Asn Gly		
530	535	540
Ala Thr Ala Gly Asn Gly Asp Asp Gly Leu Ile Pro Pro Arg Lys Ser		
545	550	555
Arg Thr Pro Glu Ser Gln Gln Phe Pro Asp Thr Glu Asn Glu Glu Tyr		
565	570	575
His Ser Asp Glu Gln Asn Asp Thr Gln Lys Gln Phe Cys Glu Glu Gln		
580	585	590
Asn Thr Gly Ile Leu His Asp Glu Ile Leu Ile His Glu Glu Lys Gln		
595	600	605
Ile Glu Val Val Glu Lys Met Asn Ser Glu Leu Ser Leu Ser Cys Lys		
610	615	620
Lys Glu Lys Asp Ile Leu His Glu Asn Ser Thr Leu Arg Glu Glu Ile		
625	630	635
Ala Met Leu Arg Leu Glu Leu Asp Thr Met Lys His Gln Ser Gln Leu		
645	650	655

&lt;210&gt; 380

&lt;211&gt; 671

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 380

Met Val Val Glu Val Asp Ser Met Pro Ala Ala Ser Ser Val Lys Lys	
1	5
Pro Phe Gly Leu Arg Ser Lys Met Gly Lys Trp Cys Cys Arg Cys Phe	
20	25
Pro Cys Cys Arg Glu Ser Gly Lys Ser Asn Val Gly Thr Ser Gly Asp	
35	40
His Asp Asp Ser Ala Met Lys Thr Leu Arg Ser Lys Met Gly Lys Trp	
50	55
Cys Arg His Cys Phe Pro Cys Cys Arg Gly Ser Gly Lys Ser Asn Val	
65	70
Gly Ala Ser Gly Asp His Asp Asp Ser Ala Met Lys Thr Leu Arg Asn	
85	90
Lys Met Gly Lys Trp Cys Cys His Cys Phe Pro Cys Cys Arg Gly Ser	
100	105
	110

Gly	Lys	Ser	Lys	Val	Gly	Ala	Trp	Gly	Asp	Tyr	Asp	Asp	Ser	Ala	Phe
	115						120					125			
Met	Glu	Pro	Arg	Tyr	His	Val	Arg	Gly	Glu	Asp	Leu	Asp	Lys	Leu	His
	130						135					140			
Arg	Ala	Ala	Trp	Trp	Gly	Lys	Val	Pro	Arg	Lys	Asp	Leu	Ile	Val	Met
	145					150					155				160
Leu	Arg	Asp	Thr	Asp	Val	Asn	Lys	Lys	Asp	Lys	Gln	Lys	Arg	Thr	Ala
				165					170						175
Leu	His	Leu	Ala	Ser	Ala	Asn	Gly	Asn	Ser	Glu	Val	Val	Lys	Leu	Leu
			180					185						190	
Leu	Asp	Arg	Arg	Cys	Gln	Leu	Asn	Val	Leu	Asp	Asn	Lys	Lys	Arg	Thr
		195					200					205			
Ala	Leu	Ile	Lys	Ala	Val	Gln	Cys	Gln	Glu	Asp	Glu	Cys	Ala	Leu	Met
	210					215					220				
Leu	Leu	Glu	His	Gly	Thr	Asp	Pro	Asn	Ile	Pro	Asp	Glu	Tyr	Gly	Asn
	225					230					235				240
Thr	Thr	Leu	His	Tyr	Ala	Ile	Tyr	Asn	Glu	Asp	Lys	Leu	Met	Ala	Lys
				245					250						255
Ala	Leu	Leu	Leu	Tyr	Gly	Ala	Asp	Ile	Glu	Ser	Lys	Asn	Lys	His	Gly
			260					265					270		
Leu	Thr	Pro	Leu	Leu	Leu	Gly	Val	His	Glu	Gln	Lys	Gln	Gln	Val	Val
		275					280						285		
Lys	Phe	Leu	Ile	Lys	Lys	Lys	Ala	Asn	Leu	Asn	Ala	Leu	Asp	Arg	Tyr
	290					295					300				
Gly	Arg	Thr	Ala	Leu	Ile	Leu	Ala	Val	Cys	Cys	Gly	Ser	Ala	Ser	Ile
	305					310					315				320
Val	Ser	Leu	Leu	Leu	Glu	Gln	Asn	Ile	Asp	Val	Ser	Ser	Gln	Asp	Leu
				325					330					335	
Ser	Gly	Gln	Thr	Ala	Arg	Glu	Tyr	Ala	Val	Ser	Ser	His	His	His	Val
			340					345					350		
Ile	Cys	Gln	Leu	Leu	Ser	Asp	Tyr	Lys	Glu	Lys	Gln	Met	Leu	Lys	Ile
		355					360					365			
Ser	Ser	Glu	Asn	Ser	Asn	Pro	Glu	Gln	Asp	Leu	Lys	Leu	Thr	Ser	Glu
		370				375					380				
Glu	Glu	Ser	Gln	Arg	Phe	Lys	Gly	Ser	Glu	Asn	Ser	Gln	Pro	Glu	Lys
					390					395					400
Met	Ser	Gln	Glu	Pro	Glu	Ile	Asn	Lys	Asp	Gly	Asp	Arg	Glu	Val	Glu
				405					410						415
Glu	Glu	Met	Lys	Lys	His	Glu	Ser	Asn	Asn	Val	Gly	Leu	Leu	Glu	Asn
			420					425					430		
Leu	Thr	Asn	Gly	Val	Thr	Ala	Gly	Asn	Gly	Asp	Asn	Gly	Leu	Ile	Pro
		435					440					445			
Gln	Arg	Lys	Ser	Arg	Thr	Pro	Glu	Asn	Gln	Gln	Phe	Pro	Asp	Asn	Glu
						450					460				
Ser	Glu	Glu	Tyr	His	Arg	Ile	Cys	Glu	Leu	Val	Ser	Asp	Tyr	Lys	Glu
					470					475					480
Lys	Gln	Met	Pro	Lys	Tyr	Ser	Ser	Glu	Asn	Ser	Asn	Pro	Glu	Gln	Asp
				485					490					495	
Leu	Lys	Leu	Thr	Ser	Glu	Glu	Glu	Ser	Gln	Arg	Leu	Glu	Gly	Ser	Glu
			500					505					510		
Asn	Gly	Gln	Pro	Glu	Lys	Arg	Ser	Gln	Glu	Pro	Glu	Ile	Asn	Lys	Asp
		515					520					525			
Gly	Asp	Arg	Glu	Leu	Glu	Asn	Phe	Met	Ala	Ile	Glu	Glu	Met	Lys	Lys
	530					535						540			
His	Gly	Ser	Thr	His	Val	Gly	Phe	Pro	Glu	Asn	Leu	Thr	Asn	Gly	Ala
				545		550				555					560
Thr	Ala	Gly	Asn	Gly	Asp	Asp	Gly	Leu	Ile	Pro	Pro	Arg	Lys	Ser	Arg
				565					570						575



Thr Pro Glu Ser Gln Gln Phe Pro Asp Thr Glu Asn Glu Glu Tyr His  
                     580                    585                    590  
 Ser Asp Glu Gln Asn Asp Thr Gln Lys Gln Phe Cys Glu Glu Gln Asn  
                     595                    600                    605  
 Thr Gly Ile Leu His Asp Glu Ile Leu Ile His Glu Glu Lys Gln Ile  
                     610                    615                    620  
 Glu Val Val Glu Lys Met Asn Ser Glu Leu Ser Leu Ser Cys Lys Lys  
                     625                    630                    635                    640  
 Glu Lys Asp Ile Leu His Glu Asn Ser Thr Leu Arg Glu Glu Ile Ala  
                     645                    650                    655  
 Met Leu Arg Leu Glu Leu Asp Thr Met Lys His Gln Ser Gln Leu  
                     660                    665                    670

<210> 381  
 <211> 251  
 <212> DNA  
 <213> Homo sapien

<400> 381  
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 ccaatatccc aggagaagca ttggggaggt gggggcaggt gaaggacca ggactcacac 180  
 atctggggcc tccaaggcag aggagaggggt cctcaagaag gtcaggagga aaatccgtaa 240  
 caagcagtca g 251

<210> 382  
 <211> 3279  
 <212> DNA  
 <213> Homo sapiens

<400> 382  
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 atgctggagg gtgtcaggaa gtgatcgggc tctggggcag ggaggagggg tggggagtg 120  
 cactgggagg ggacatcctg cagaaggtag gagtgcagaa acacccgctg caggggaggg 180  
 gagagccctg cggcacctgg gggagcagag ggagcagcac ctgcccaggc ctgggaggag 240  
 gggcctggag ggcgtgagga ggagcgaggg ggctgcatgg ctggagtgag ggatcagggg 300  
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 gccacaggag gacactgctt ttctctctgag gagtgcaggag ctgtggatgg tgcaggacag 420  
 aagaaggaca gggcctggct caggtgtcca gaggtgtcg ctggcttccc ttggggatca 480  
 gactgcaggg agggagggcg gcagggttgt gggggagtg acgatgagga tgacctgggg 540  
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 cctcagtctc tcccctccac tccatcctcc atctggcctc agtgggtcat tctgatcact 660  
 gaactgacca taccagccc tgcccacggc cctccatggc tcccaatgc cctggagagg 720  
 ggacatctag tcagagagta gtccatgaaga ggtggcctct gcgatgtgcc tgtgggggca 780  
 gcatcctgca gatggtcccg gccctcatcc tgcagacctg tctgcaggga ctgtcctcct 840  
 ggaccttgcc ccttgtgcag gagctggacc ctgaagtccc ctcccatag gccaaagactg 900  
 gaggcttggt ccctctgttg gactccctgc ccatattctt gtgggagtggt gttctggaga 960  
 catttctgtc tgttctctgag agctgggaat tgcctcaggt catctgcctg cgcgggtctg 1020  
 agagatggag ttgcctaggc agttattggg gccaatcttt ctactgtgt ctctcctcct 1080  
 ttacccttag ggtgattctg ggggtccact tgcctgtaat ggtgtgcttc aaggtatcac 1140  
 atcatggggc cctgagccat gtgcctgcc tgaagaagcct gctgtgtaca ccaaggtggt 1200  
 gcattaccgg aagtggatca aggacacat cgagccaac ccctgagtgc ccctgtccca 1260  
 cccctacctc tagtaaatat aagtccacct cacgttctgg catcacttgg cctttctgga 1320  
 tgcctggacac ctgaagcttg gaactcacct ggccgaagct cgagcctcct gactcctact 1380  
 gacctgtgct ttctgtgtg gagtccaggg ctgctaggaa aaggaatggg cagacacagg 1440  
 tgtatgccaa tgtttctgaa atgggtataa ttctgcctc tccttcggaa cactggctgt 1500  
 ctctgaagac ttctcgctca gtttcagtga ggacacacac aaagacgtgg gtgacctagt 1560  
 tgtttgtggg gtgcagagat gggaggggtg gggccacccc tggaaagagt gacagtgaca 1620

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caaggtggac actctctaca gatcactgag gataagctgg agccacaatg catgaggcac 1680
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aaagaagaat ccagaaatag gggcacattg aggaatgata ctgagcccaa agagcattca 2760
atcattgttt tatttgcctt cttttcacac cattggtgag ggagggatta ccaccctggg 2820
gttatgaaga tggttgaaca cccacacat agcaccggag atatgagatc aacagtttct 2880
tagccataga gattcacagc ccagagcagg aggacgctgc acaccatgca ggatgacatg 2940
ggggatgcgc tcgggatttg tgtgaagaag caaggactgt tagaggcagg ctttatagta 3000
acaagacggt ggggcaaact ctgatttccg tgggggaatg tcatggtctt gctttactaa 3060
gttttgagac tggcaggtag tgaaactcat taggctgaga accttgtgga atgcagctga 3120
cccagctgat agaggaaagta gccaggtggg agcctttccc agtgggtgtg ggacatatct 3180
ggcaagattt tgtggcactc ctggttacag atactggggc agcaaataaa actgaatctt 3240
gttttcagac cttaaaaaaa aaaaaaaaaa aaaagtttt 3279

```

&lt;210&gt; 383

&lt;211&gt; 154

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 383

```

Met Ala Gly Val Arg Asp Gln Gly Gln Gly Ala Arg Trp Pro His Thr
          5                      10                      15

```

```

Gly Lys Arg Gly Pro Leu Leu Gln Gly Leu Thr Trp Ala Thr Gly Gly
          20                      25                      30

```

```

His Cys Phe Ser Ser Glu Glu Ser Gly Ala Val Asp Gly Ala Gly Gln
          35                      40                      45

```

```

Lys Lys Asp Arg Ala Trp Leu Arg Cys Pro Glu Ala Val Ala Gly Phe
          50                      55                      60

```

```

Pro Leu Gly Ser Asp Cys Arg Glu Gly Gly Arg Gln Gly Cys Gly Gly
          65                      70                      75                      80

```

```

Ser Asp Asp Glu Asp Asp Leu Gly Val Ala Pro Gly Leu Ala Pro Ala
          85                      90                      95

```

```

Trp Ala Leu Thr Gln Pro Pro Ser Gln Ser Pro Gly Pro Gln Ser Leu
          100                     105                     110

```

```

Pro Ser Thr Pro Ser Ser Ile Trp Pro Gln Trp Val Ile Leu Ile Thr
          115                     120                     125

```

Glu Leu Thr Ile Pro Ser Pro Ala His Gly Pro Pro Trp Leu Pro Asn  
 130 135 140

Ala Leu Glu Arg Gly His Leu Val Arg Glu  
 145 150

<210> 384  
 <211> 557  
 <212> DNA  
 <213> Homo sapiens

<400> 384  
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 aaagatgtgt tttgttttgg actctctgtg gtcccttcca atgctgtggg tttccaacca 120  
 ggggaagggt cccttttgca ttgccaagt ccataacat gagcactact ctaccatggg 180  
 tctgcctcct ggccaagcag gctggttgc aagaatgaaa tgaatgattc tacagctagg 240  
 acttaacctt gaaatggaaa gtcttgcaat cccatttgca ggatccgtct gtgcacatgc 300  
 ctctgtagag agcagcattc ccagggacct tggaaacagt tggcactgta aggtgcttgc 360  
 tccccaagac acatcctaaa aggtgttgta atggtgaaaa cgtcttcctt ctttattgcc 420  
 ccttcttatt tatgtgaaca actgtttgtc tttttttgta tcttttttaa actgtaaaag 480  
 tcaattgtga aatgaatat catgcaaata aattatgcga ttttttttc aaagtaaaaa 540  
 aaaaaaaaa aaaaaaa 557

<210> 385  
 <211> 337  
 <212> DNA  
 <213> Homo sapiens

<400> 385  
 ttcccagtg atgtgcgagg gaagacacat ttactatcct tgatggggct gattccttta 60  
 gtttctctag cagcagatgg gttaggagga agtgaccaa gtggttgact cctatgtgca 120  
 tctcaaagcc atctgtgtc ttcgagtacg gacacatcat cactcctgca ttgttgatca 180  
 aaacgtggag gtgcttttcc tcagctaaga agcccttagc aaaagctcga atagacttag 240  
 tatcagacag gtccagttc cgcaccaaca cctgtggtt ccctgtcgtg gtctggatct 300  
 ctttgccac caattcccc tttccacat cccgca 337

<210> 386  
 <211> 300  
 <212> DNA  
 <213> Homo sapiens

<400> 386  
 gggcccgccta ccggcccagg cccgcctcg cgagtcctcc tccccgggtg cctgcccga 60  
 gccgctcgg ccagagggt gggcgggg ctgctctac cggtggcg ctgtaactca 120  
 gcgaccttg ccgaaggct ctagcaagga cccaccgacc ccagccgcg cggcgcggc 180  
 gcggactttg ccggtgtgt gggcgggagc ggactgcgtg tccgaggacg ggcagcgaag 240  
 atgttagcct tcgctgccag gaccgtggac cgatcccagg gctgtggtgt aacctcagcc 300

<210> 387  
 <211> 537  
 <212> DNA  
 <213> Homo sapiens

<400> 387  
 gggccgagtc gggcaccaag ggactctttg caggcttctt tcctcggatc atcaaggctg 60  
 cccctcctg tgccatcatg atcagacct atgagttcgg caaaagcttc ttccagaggc 120

```

tgaaccagga ccggttctg ggcggctgaa aggggcaagg aggcaaggac cccgtctctc 180
ccacggatgg ggagagggca ggaggagacc cagccaagtg ctttttcctc agcactgagg 240
gagggggctt gtttcccttc cctcccggcg acaagctcca gggcagggtt gtccctctgg 300
gcggcccagc acttcctcag acacaacttc ttctgctgctg tccagtcgtg gggatcatca 360
cttaccacc cccaagtctc aagaccaaat cttccagctg cccccttcgt gtttccctgt 420
gtttgctgta gctgggcatg tctccaggaa ccaagaagcc ctcagcctgg tgtagtctcc 480
ctgacccttg ttaattcctt aagtctaaag atgatgaact tcaaaaaaaaa aaaaaaa 537

```

&lt;210&gt; 388

&lt;211&gt; 520

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 388

```

aggataatTT ttaaaccaat caaatgaaaa aaacaaacaa acaaaaaagg aaatgtcatg 60
tgaggTTaaa ccagtttgca ttcccctaata gtggaaaaag taagaggact actcagcact 120
gtttgaagat tgctcttctt acagcttctg agaatttgtt tatttcactt gccaaagtga 180
ggaccccttc cccaacatgc cccagcccac ccctaagcat ggtcccttgt caccaggcaa 240
ccaggaaact gctacttgtg gacctcacca gagaccagga gggtttggtt agctcacagg 300
acttccccca cccagaaga ttagcatccc atactagact cataactcaac tcaactaggc 360
tcatactcaa ttgatgggta ttagacaatt ccatttcttt ctgggttatta taaacagaaa 420
atctttcctc ttctcattac cagtaaaggc tcttggtatc tttctgttgg aatgatttct 480
atgaacttgt cttattttta tggtggggtt tttttctggt 520

```

&lt;210&gt; 389

&lt;211&gt; 365

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 389

```

cgttgcccc gtttgacaga aggaaaggcg gagcttattc aaagtctaga gggagtggag 60
gagTTaaggc tggatttcag atctgcctgg ttccagccgc agtgtgccct ctgctcccc 120
aacgactttc caaataatct caccagcgcc ttccagctca ggcgtcctag aagcgtcttg 180
aagcctatgg ccagctgtct ttgtgttccc tctcacccgc ctgtcctcac agctgagact 240
cccaggaaac cttcagacta ccttcctctg ccttcagcaa ggggcgttgc ccacattctc 300
tgagggtcag tggagaagcc tagactccca ttgctagagg tagaaagggg aagggtgctg 360
gggag 365

```

&lt;210&gt; 390

&lt;211&gt; 221

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(221)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 390

```

tgccttcca tcctggcccc gacttctctg tcaggaaagt ggggatggac cccatctgca 60
tacacgntt ctcatgggtg tggacatct ctgcttgccg ttccaggaag gcctctggct 120
gctctangag tctgancnga ntcgttgccc cantntgaca naaggaaagg cggagcttat 180
tcaaagtcta gagggagtgg aggagttaag gctggatttc a 221

```

&lt;210&gt; 391

&lt;211&gt; 325

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(325)  
<223> n = A,T,C or G

<400> 391  
tggagcaggt cccgaggcct ccctagagcc tggggccgac tctgtgncga tgcangcttt 60  
ctctcgcgcc cagcctggag ctgctcctgg catctaccaa caatcagncg aggcgagcag 120  
tagccagggc actgctgcca acagccagtc cnnataccat catgtnaccc ggtgngctct 180  
naanttingat ntccanagcc ctacccatcn tagttctgct ctcccaccgg ntaccagccc 240  
cactgcccag gaatcctaca gccagtaccc tgtcccgacg tctctaccta ccagtacgat 300  
gagacctccg gctactacta tgacc 325

<210> 392  
<211> 277  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(277)  
<223> n = A,T,C or G

<400> 392  
atattgttta actccttccct ttatatcttt taacattttc atggngaaaag gttcacatct 60  
agtctcaact nggcnagn gn ctccacttg agtctcttcc ccggcctggn ccagtnгнаа 120  
antaccanga accgncatgn cttanaaаcn ncctggtttn tgggttnntc aatgactgca 180  
tgcagtgcac caccctgtcc actacgtgat gctgtaggat taaagtctca cagtgggcgg 240  
ctgaagatac agcgccgcgt cctgtgttgc tggggaa 277

<210> 393  
<211> 566  
<212> DNA  
<213> Homo sapiens

<400> 393  
actagtccag tgtggtggaa ttcgcggccg cgtcgacgga caggtcagct gtctggctca 60  
gtgatctaca ttctgaagtt gtctgaaaat gtcttcatga ttaaattcag cctaaacggt 120  
ttgccgggaa cactgcagag acaatgctgt gagtttccaa ccttagccca tctgcgggca 180  
gagaaggtct agtttgcca tcagcattat catgatatca ggactgggta cttgggtaag 240  
gaggggtcta ggagatctgt cccttttaga gacaccttac ttataatgaa gtatttgga 300  
gggtggtttt caaaagtaga aatgtcctgt attccgatga tcatcctgta aacattttat 360  
catttattaa tcatccctgc ctgtgtctat tattatattc atatctctac gctggaaact 420  
ttctgcctca atgtttactg tgcctttgtt tttgctagtt tgtgttggtg aaaaaaaaaa 480  
cattctctgc ctgagtttta atttttgtcc aaagttattt taatctatac aattaaaagc 540  
ttttgcctat caaaaaaaaaa aaaaaa 566

<210> 394  
<211> 384  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(384)  
<223> n = A,T,C or G

&lt;400&gt; 394

```

gaacatacat gtcccgccac ctgagctgca gtctgacatc atcgccatca cgggcctcgc 60
tgcaaatng gaccgggcca aggctggact gctggagcgt gtgaaggagc tacaggccna 120
gcaggaggac cgggctttaa ggagttttaa gctgagtgct actgtagacc ccaaatacca 180
tcccaagatt atcgggagaa agggggcagt aattacccaa atccggttgg agcatgacgt 240
gaacatccag tttcctgata aggacgatgg gaaccagccc caggaccaa ttaccattac 300
agggtacgaa aagaacacag aagctgccag ggatgctata ctgagaattg tgggtgaact 360
tgagcagatg gtttctgagg acgt 384

```

&lt;210&gt; 395

&lt;211&gt; 399

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 395

```

ggcaaaactg tgtgacctca ataagacctc gcagatccaa ggtcaagtat cagaagtgc 60
tctgaccttg gactccaaga cctacatcaa cagcctggct atattagatg atgagccagt 120
tatcagaggt ttcattcatt cggaattgtt ggagtctaag gaaatcatgg cctctgaagt 180
attcagctct ttcagtagcc ctgagttctc tatagagttg cctaacacag gcagaattgg 240
ccagctactt gtctgcaatt gtatcttcaa gaataccctg gccatccctt tgactgacgt 300
caagttctct ttggaaagcc tgggcatctc ctactacag acctctgacc atgggacggt 360
gcagcctggt gagaccatcc aatcccaaat aaaatgcac 399

```

&lt;210&gt; 396

&lt;211&gt; 403

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(403)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 396

```

tggagttntc agtgcaaaca agccataaag cttcagtagc aaattactgt ctcacagaaa 60
gacattttca acttctgctc cagctgctga taaaacaaat catgtgttta gcttgactcc 120
agacaaggac aacctgttcc ttcataactc tctagagaaa aaaaggaggt gttagtagat 180
actaaaaaaa gtggatgaat aatctggata tttttcctaa aaagattcct tgaaacacat 240
taggaaaatg gagggcctta tgatcagaat gctagaatta gtccattgtg ctgaagcagg 300
gtttagggga gggagtggag gataaaagaa ggaaaaaag aagagtgaga aaacctattt 360
atcaaagcag gtgctatcac tcaatgtag gccctgctct ttt 403

```

&lt;210&gt; 397

&lt;211&gt; 100

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(100)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 397

```

actagtnacg tgtgggtggaa ttcgcggccg cgtcgaccta naanccatct ctatagcaaa 60
tccatccccg ctctgtgttg gtnacagaat gactgacaaa 100

```

&lt;210&gt; 398

&lt;211&gt; 278

<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(278)  
<223> n = A,T,C or G

<400> 398  
gcggccgcgt cgacagcagt tccgccagcg ctgcgccctg ggtggggatg tgctgcacgc 60  
ccacctggac atctggaagt cagcggcctg gatgaaagag cggacttcac ctggggcgat 120  
tcactactgt gcctcgacca gtgaggagag ctggaccgac agcgagggtg actcatcatg 180  
ctccgggcag cccatccacc tgtggcagtt cctcaaggag ttgctactca agccccacag 240  
ctatggccgc ttcat tangt ggtcaacaa ggagaagg 278

<210> 399  
<211> 298  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(298)  
<223> n = A,T,C or G

<400> 399  
acggagggtg aggaagcgnc cctgggatcg anaggatggg tcctgncatt gaccncctcn 60  
gggggtgccng catggagcgc atgggcgcgg gcctgggcca cggcatggat cgcggtgggt 120  
ccgagatcga gcgcattggc ctggtcatgg accgcatggg ctccgtggag cgcatgggt 180  
ccggcattga gcgcattggc ccgctgggcc tcgaccacat ggctccanc attgancga 240  
tgggccagac catggagcgc attggctctg cgtggagcn catgggtgcc ggcatggg 298

<210> 400  
<211> 548  
<212> DNA  
<213> Homo sapiens

<400> 400  
acatcaacta cttcctcatt ttaaggatg gcagttccct tcatccctt ttctgcctt 60  
gtacatgtac atgtatgaaa ttctcttctc ttaccgaact ctctccacac atcacaagg 120  
caaagaacca cacgcttaga agggtaagag ggcaccctat gaaatgaaat ggtgatttct 180  
tgagtctctt ttttccacgt ttaaggggcc atggcaggac ttagagttgc gagttaagac 240  
tgcagagggc tagagaatta tttcatacag gctttgaggc caccatgtc acttatcccg 300  
tataccctct caccatcccc ttgtctactc tgatgcccc aagatgcaac tgggcagcta 360  
gttggcccca taattctggg cctttgttgt ttgttttaat tacttgggca tcccaggaag 420  
ctttccagtg atctcctacc atgggcccc ctccctggat caagccctc ccaggccctg 480  
tccccagccc ctccctgccc agcccacccg cttagccttg tgctcagccc tccattggg 540  
agcaggtt 548

<210> 401  
<211> 355  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(355)  
<223> n = A,T,C or G

<400> 401  
actgtttcca tggtatgttt ctacacattg ctacctcagt gtccttgaa acttagcttt 60  
tgatgtctcc aagtagtcca ccttcattta actctttgaa actgtatcat ctttgccaag 120  
taagagtggg ggcctatttc agctgctttg acaaaatgac tggctcctga cttaacgttc 180  
tataaatgaa tgtgtgaag caaagtgtcc atggtggcgg cgaagaagan aaagatgtgt 240  
tttgttttgg actctctgtg gtcccttcca atgctgnggg tttccaacca ggggaagggt 300  
cccttttgca ttgccaagtg ccataacctg gagcactact ctaccatggn tctgc 355

<210> 402  
<211> 407  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(407)  
<223> n = A,T,C or G

<400> 402  
atggggcaag ctggataaag aaccaagacc cactggagta tgctgtcttc aagaaaccca 60  
tctcacatgc ggtggcatac ataggctcaa aataaaggaa tggagaaaaa tatttcaagc 120  
aatggaataa cagaaaaaag caggtgttgc actcctactt tctgacaaaa cagactatgc 180  
gaataaagat aaaaaagaga aggacattac aaaggtggtc ctgacctttg ataaatctca 240  
ttgcttgata ccaacctggg ctgttttaat tgcccaaacc aaaaggataa tttgctgagg 300  
ttgtggagct tctccctgc agagagtccc tgatctccca aaatttggtt gagatgtaag 360  
gntgattttg ctgacaactc cttttctgaa gttttactca ttccaa 407

<210> 403  
<211> 303  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(303)  
<223> n = A,T,C or G

<400> 403  
cagtatttat agccnaactg aaaagctagt agcaggcaag tctcaaattcc aggcaccaa 60  
tcctaagcaa gagccatggc atggtgaaaa tgcaaaagga gagtctggcc aatctacaaa 120  
tagagaacaa gacctactca gtcataaaca aaaaggcaga caccaacatg gatctcatgg 180  
gggattggat attgtaatta tagagcagga agatgacagt gatcgatcatt tggcacaaca 240  
tcttaacaac gaccgaaacc cattatttac ataaacctcc attcggtaac catgttgaaa 300  
gga 303

<210> 404  
<211> 225  
<212> DNA  
<213> Homo sapiens

<400> 404  
aagtgtact tttaaaaatt tagtggattt tgaaaattct tagaggaaag taaaggaaaa 60  
attgttaatg cactcattta cctttacatg gtgaaagttc tctcttgatc ctacaacag 120  
acattttcca ctggtgttgc catagttgtt aagtgatca gatgtgttgg gcatgtgaat 180  
ctccaagtgc ctgtgtaata aataaagtat ctttatttca ttcat 225

<210> 405



<211> 334  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(334)  
<223> n = A,T,C or G

<400> 405  
gagctgttat actgtgagtt ctactaggaa atcatcaaat ctgagggttg tctggaggac 60  
ttcaatacac ctcccccat agtgaatcag cttccagggg gtccagtccc tctccttact 120  
tcatccccat cccatgccaa aggaagaccc tccctccttg gctcacagcc ttctctagge 180  
ttccagtgct ctccaggaca gagtgggtta tgttttcagc tccatccttg ctgtgagtgt 240  
ctggtgcggt tgtgcctoca gcttctgctc agtgcttcat ggacagtgtc cagcccatgt 300  
cactctccac tctctcanng tggatcccac ccct 334

<210> 406  
<211> 216  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(216)  
<223> n = A,T,C or G

<400> 406  
tttcatacct aatgaggag ttganatnac atnnaaccag gaaatgcatg gatctcaang 60  
gaaacaaaca cccaataaac tcggagtggc agactgacaa ctgtgagaca tgcacttgct 120  
acnaaacaca aatttnatgt tgcacccttg tttctacacc tgtgggttat gacaaagaca 180  
actgccaaag aatnttcaag aaggaggact gccant 216

<210> 407  
<211> 413  
<212> DNA  
<213> Homo sapiens

<400> 407  
gctgacttgc tagtatcatc tgcattcatt gaagcacaag aacttcatgc cttgactcat 60  
gtaaatgcaa taggattaaa aaataaattt gatatcacat ggaaacagac aaaaaatatt 120  
gtacaacatt gcacccagtg tcagattcta cacctggcca ctcaggaagc aagagttaat 180  
cccagaggtc tatgtcctaa tgtgttatgg caaatggatg tcatgcacgt accttcattt 240  
ggaaaattgt catttgtoca tgtgacagtt gatacttatt cacatttcat atgggcaacc 300  
tgccagacag gagaaagtct tcccatgtta aaagacattt attatcttgt tttcctgtca 360  
tgggagttcc agaaaaagtt aaaacagaca atgggccagg ttctgtagta aag 413

<210> 408  
<211> 183  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(183)  
<223> n = A,T,C or G

<400> 408

```
ggagctngcc ctcaattcct ccatntctat gttancatat ttaatgtctt ttgnnattaa 60
tncettaacta gttaatcctt aaagggtan ntaatcotta actagtcctt ccattgtgag 120
cattatcctt ccagtattcn cttctnttt tatttactcc ttcctggcta cccatgtact 180
ntt 183
```

<210> 409

<211> 250

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_feature

<222> (1)...(250)

<223> n = A,T,C or G

<400> 409

```
cccacgcatg ataagctctt tatttctgta agtcctgcta ggaaatcatc aaatctgacg 60
gtgggtttggg ggacctgaac aaacctcctg taattaatca gctttcagtt tctcccccta 120
gtccctcctt caacaacata ggaggatcct ccccttcttt ctgctcacgg cttatctag 180
gcttcccagt gcccccagga cagcgtgggc tatgtttaca gcgntcctt gctggggggg 240
ggcctatgc 250
```

<210> 410

<211> 306

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_feature

<222> (1)...(306)

<223> n = A,T,C or G

<400> 410

```
ggctggtttg caagaatgaa atgaatgatt ctacagctag gacttaacct tgaaatggaa 60
agtcttgcaa tccatttgc aggatccgtc tgtgcacatg cctctgtaga gagcagcatt 120
cccagggacc ttggaaacag ttggcactgt aaggtgcttg ctccccaaga cacatcctaa 180
aaggtgttgt aatggtgaaa accgcttctt tctttattgc cccttcttat ttatgtgaac 240
nactggttg ctttttttgn atcttttta aactggaaag ttcaattgng aaaatgaata 300
tentgc 306
```

<210> 411

<211> 261

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_feature

<222> (1)...(261)

<223> n = A,T,C or G

<400> 411

```
agagatattn cttaggtnaa agttcataga gttcccatga actatatgac tggccacaca 60
ggatcttttg tatttaagga ttctgagatt ttgcttgagc aggattagat aaggctgttc 120
tttaaagtgc tgaaatggaa cagatttcaa aaaaaaaccc cacaatctag ggtgggaaca 180
aggaaggaaa gatgtgaata ggctgatggg caaaaaacca atttaccat cagttccagc 240
cttctctcaa ggngaggcaa a 261
```

<210> 412

<211> 241  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(241)  
 <223> n = A,T,C or G

<400> 412  
 gttcaatggt acctgacatt tctacaacac ccactcacc gatgtattcg ttgccagtg 60  
 ggaacatacc agcctgaatt tggaaaaaat aattgtgttt cttgccagg aaatactacg 120  
 actgactttg atggctccac aaacataacc cagtgtaaaa acagaagatg tggaggggag 180  
 ctgggagatt tctactggga cattgaattc ccaaactacc cangcaatta cccagccaac 240  
 a 241

<210> 413  
 <211> 231  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(231)  
 <223> n = A,T,C or G

<400> 413  
 aactcttaca atccaagtga ctcactctgtg tgcttgaatc ctttccactg tctcatctcc 60  
 ctcactcaag tttctagtag cttctctttg ttgtgaagga taatcaaact gaacaacaaa 120  
 aagtttactc tctctatttg gaacctaaaa actctcttct tcttgggtct gagggtctca 180  
 agaatccttg aatcanttct cagatcattg gggacaccan atcaggaacc t 231

<210> 414  
 <211> 234  
 <212> DNA  
 <213> Homo sapiens

<400> 414  
 actgtccatg aagcactgag cagaagctgg aggcacaacg caccagacac tcacagcaag 60  
 gatggagctg aaaacataac ccactctgtc ctggaggcac tgggaagcct agagaaggct 120  
 gtgagccaag gagggagggt cttccttttg catgggatgg ggatgaagta aggagaggga 180  
 ctggaccccc tggaagctga ttcactatgg ggggagggtg attgaagtcc tcca 234

<210> 415  
 <211> 217  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(217)  
 <223> n = A,T,C or G

<400> 415  
 gcataggatt aagactgagt atcttttcta cattctttta actttctaag gggcacttct 60  
 caaacacag accaggtagc aaatctccac tgctctaagg ntctcaccac cactttctca 120  
 cacctagcaa tagtagaatt cagtctact tctgaggcca gaagaatggg tcagaaaaat 180  
 antggattat aaaaaataac aattaagaaa aataatc 217

<210> 416  
<211> 213  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(213)  
<223> n = A,T,C or G

<400> 416  
atgcataat aaagganact gcctcgcttt tagaagacat ctggncgtgt ctctgcatga 60  
ggcacagcag taaagctctt tgattcccag aatcaagaac tctccccttc agactattac 120  
cgaatgcaag gtggttaatt gaaggccact aattgatgt caaatagaag gatattgact 180  
atattggaac agatggagtc tctactacaa aag 213

<210> 417  
<211> 303  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(303)  
<223> n = A,T,C or G

<400> 417  
nagtcttcag gcccatcagg gaagttcaca ctggagagaa gtcatacata tgtactgtat 60  
gtgggaaagg ctttactctg agttcaaact ttcaagccca tcagagagtc cacactggag 120  
agaagccata caaatgcaat gagtgtggga agagcttcag gagggattcc cattatcaag 180  
ttcatctagt ggtccacaca ggagagaaac cctataaatg tgagatatgt gggaagggt 240  
tcantcaaag ttcgtatctt caaatccatc ngaaggncca cagtatanan aaacctttta 300  
agt 303

<210> 418  
<211> 328  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(328)  
<223> n = A,T,C or G

<400> 418  
tttttggcgg tgggtgggca gggacgggac angagtctca ctctgttgcc caggctggag 60  
tgcacaggca tgatctcggc tcaactacaac ccctgcctcc catgtccaag cgattcttgt 120  
gcctcagcct tccctgtagc tagaattaca ggcacatgcc accacacca gctagttttt 180  
gtatttttag tagagacagg gtttcacat gttggccagg ctggtctcaa actcctnacc 240  
tcagnggtca ggctggtctc aaactcctga cctcaagtga tctgcccacc tcagcctccc 300  
aaagtgtan gattacaggc cgtgagcc 328

<210> 419  
<211> 389  
<212> DNA  
<213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(389)  
 <223> n = A,T,C or G

<400> 419  
 cctcctcaag acggcctgtg gtccgcctcc cggcaaccaa gaagcctgca gtgccatatg 60  
 acccctgagc catggactgg agcctgaaag gcagcgtaca ccctgctcct gatcttgctg 120  
 cttgtttcct ctctgtggct ccattcatag cacagtgtgt gcactgaggc ttgtgcaggc 180  
 cgagcaaggc caagctggct caaagagcaa ccagtcaact ctgccacggc gtgccaggca 240  
 ccggttctcc agccaccaac ctactcgcct cccgcaaagc gcacatcagt tcttctaccc 300  
 taaaggtagg accaaagggc atctgctttt ctgaagtctc ctgctctatc agccatcacg 360  
 tggcagccac tcnggctgtg tcgacgcgg 389

<210> 420  
 <211> 408  
 <212> DNA  
 <213> Homo sapiens

<400> 420  
 gttcctccta actcctgcca gaaacagctc tcctcaacat gagagctgca cccctcctcc 60  
 tggccagggc agcaagcctt agccttggct tcttgtttct gctttttttc tggctagacc 120  
 gaagtgtact agccaaggag ttgaagtgtg tgactttggt gtttcggcat ggagaccgaa 180  
 gtcccattga cacctttccc actgacccca taaaggaatc ctcatggcca caaggatttg 240  
 gccaaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataagaaaga 300  
 gatatagaaa attcttgaat gagtctata aacatgaaca ggtttatatt cgaagcacag 360  
 acgttgaccg gactttgatg aagtgcctatg acaaacctgg caagcccg 408

<210> 421  
 <211> 352  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(352)  
 <223> n = A,T,C or G

<400> 421  
 gctcaaaaat ctttttactg atnggcatgg ctacacaatc attgactatt acggaggcca 60  
 gaggagaatg aggcctggcc tgggagccct gtgcctacta naagcacatt agattatcca 120  
 ttcactgaca gaacagggtc tttttgggtc cttcttctcc accacnata acttgcatc 180  
 ctcttcttg aagattcttt ggcagttgtc tttgtcataa cccacagggt tagaaacaag 240  
 ggtgcaacat gaaatttctg tttcgtagca agtgcctgtc tcacaagttg gcangtctgc 300  
 cactccgagt ttattgggtg tttgtttcct ttgagatcca tgcatttcct gg 352

<210> 422  
 <211> 337  
 <212> DNA  
 <213> Homo sapiens

<400> 422  
 atgccacat gctggcaatg cagcgggcgg tcgaaggcct gcatatccag cccaagctgg 60  
 cgatgatcga cggcaaccgt tgcccgaagt tgccgatgcc agccgaagcg gtggtcaagg 120  
 gogatagcaa ggtgccggcg atcgcggcgg cgtcaatcct ggccaaggct agccgtgac 180  
 gtgaaatggc agctgtcgaa ttgatctacc cgggttatgg catcggcggg cataagggt 240  
 atccgacacc ggtgcacctg gaagccttgc agcggctggg gccgacgcgg attcaccgac 300  
 gcttcttccg ccggtacggc tggcctatga aaattat 337

<210> 423  
<211> 310  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(310)  
<223> n = A,T,C or G

<400> 423  
gctcaaaaat ctttttactg atatggcatg gctacacaat cattgactat tagaggccag 60  
aggagaatga ggctggcctt gggagccctg tgcctactan aagcncatta gattatccat 120  
tactgacag aacaggtctt tttgggtcc ttcttctcca ccacgatata cttgcagtcc 180  
tccttcttga agattctttg gcagttgtct ttgtcataac ccacaggtgt anaaacaagg 240  
gtgcaacatg aaatttctgt ttcgtagcaa gtgcatgtct cacagttgtc aagtctgccc 300  
tccgagttta 310

<210> 424  
<211> 370  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(370)  
<223> n = A,T,C or G

<400> 424  
gctcaaaaat ctttttactg ataggcatgg ctacacaatc attgactatt agaggccaga 60  
ggagaatgag gcctggcctg ggagccctgt gcctactaga agcacattag attatccatt 120  
cactgacaga acaggtcttt tttgggtcct ttcttctcac cagcatatac ttgcagtcc 180  
ccttcttgaa gattcttttg cagttgtctt tgtcataacc cacaggtgta gaaacatcct 240  
ggttgaatct cctggaactc cctcattag tatgaaatag catgatgcat tgcataaagt 300  
cacgaaggtg gcaaagatca caacgctgcc cagganaaca ttcattgtga taagcaggac 360  
tccgtcgacg 370

<210> 425  
<211> 216  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(216)  
<223> n = A,T,C or G

<400> 425  
aattgctatn ntatttttg ccaactcaaaa taattaccaa aaaaaaaaaa tnttaaatga 60  
taacaacnca acatcaaggn aaananaaca ggaatggntg actntgcata aatnggccga 120  
anattatcca ttatnttaag ggttgacttc aggntacagc acacagacaa acatgcccg 180  
gaggntntca ggaccgctcg atgtntntng agggagg 216

<210> 426  
<211> 596  
<212> DNA  
<213> Homo sapiens

&lt;400&gt; 426

```
cttccagtga ggataaccct gttgccccgg gccgaggttc tccattaggc tctgattgat 60
tggcagtcag tgatggaagg gtgttctgat cattccgact gccccaaggg tcgctggcca 120
gctctctgtt ttgctgagtt ggcagtagga cctaatttgt taattaagag tagatgggtga 180
gctgtccttg tattttgatt aacctaatgg ccttcccagc acgactcgga ttcagctgga 240
gacatcacgg caacttttaa tgaaatgatt tgaagggccca ttaagaggca cttcccgtta 300
ttaggcagtt catctgcact gataacttct tggcagctga gctggtcgga gctgtggccc 360
aaacgcacac ttggcttttg gttttgagat acaactctta atcttttagt catgcttgag 420
ggtggatggc cttttcagct ttaacccaat ttgcactgcc ttggaagtgt agccaggaga 480
atacactcat atactcgtgg gcttagaggg cacagcagat gtcattggtc tactgcctga 540
gtcccgctgg tcccatccca ggaccttcca tcggcgagta cctgggagcc cgtgct 596
```

&lt;210&gt; 427

&lt;211&gt; 107

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(107)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 427

```
gaagaattca agtttagttt attcaaaggg cttacngaga atcctanacc caggnccag 60
cccgggagca gccttanaga gtcctgttt gactgcccg ctcagng 107
```

&lt;210&gt; 428

&lt;211&gt; 38

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(38)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 428

```
gaacttcna anaangactt tattcactat ttacatt 38
```

&lt;210&gt; 429

&lt;211&gt; 544

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 429

```
ctttgctgga cggaataaaa gtggacgcaa gcatgacctc ctgatgaggg cgctgcattt 60
attgaagagc ggctgcagcc ctgcggttca gattaaaatc cgagaattgt atagacgccg 120
atatccacga actcttgaag gactttctga tttatccaca atcaaatcat cggttttcag 180
tttggatggg ggctcatcac ctgtagaacc tgacttggcc gtggctggaa tccactcgtt 240
gccttccact tcagttacac ctcactcacc atcctctcct gttggttctg tgctgcttca 300
agatactaag cccacatttg agatgcagca gccatctccc ccaattcctc ctgtccatcc 360
tgatgtgcag ttaaaaaatc tgccctttta tgatgtcctt gatgttctca tcaagcccac 420
gagtttagtt caaagcagta ttcagcgatt tcaagagaag ttttttattt ttgctttgac 480
acctcaacaa gttagagaga tatgcatac cagggatttt ttgccaggtg gtaggagaga 540
ttat 544
```

&lt;210&gt; 430

<211> 507  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(507)  
<223> n = A,T,C or G

<400> 430  
cttatcncaa tggggctccc aaacttggct gtgcagtgga aactccgggg gaattttgaa 60  
gaacactgac acccatcttc caccocgaca ctctgattta attgggctgc agtgagaaca 120  
gagcatcaat ttaaaaagct gcccagaatg ttntcctggg cagcgttgtg atctttgccn 180  
ccttcgtgac tttatgcaat gcatcatgct atttcatacc taatgaggga gttccaggag 240  
attcaaccag gatgttttcta cncctgtggg ttatgacaaa gacaactgcc aaagaatntt 300  
caagaaggag gactgcaagt atatcgtggg ggagaagaag gacccaaaaa agacctgttc 360  
tgtcagttaa tggataatct aatgtgcttc tagtaggcac agggctccca ggccaggcct 420  
cattctcctc tggcctctaa tagtcaatga ttgtgtagcc atgcctatca gtaaaaagat 480  
ttttgagcaa aaaaaaaaaa aaaaaaa 507

<210> 431  
<211> 392  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(392)  
<223> n = A,T,C or G

<400> 431  
gaaaattcag aatggataaa aacaaatgaa gtacaaaata tttcagattt acatagcgat 60  
aaacaagaaa gcacttatca ggaggactta caaatggaag tacactctan aaccatcatc 120  
tatcatggct aaatgtgaga ttagcacagc tgtattattt gtacattgca aacacctaga 180  
aagagatggg aaacaaaatc ccaggagttt tgtgtgtgga gtccctgggtt ttccaacaga 240  
catcattcca gcattctgag attagggnga ttggggatca ttctggagtt ggaatgttca 300  
acaaaagtga tgttgtagg taaaatgtac aacttctgga tctatgcaga cattgaaggt 360  
gcaatgagtc tggcttttac tctgctgttt ct 392

<210> 432  
<211> 387  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(387)  
<223> n = A,T,C or G

<400> 432  
ggtatccnta cataatcaaa tatagctgta gtacatgttt tcattggngt agattaccac 60  
aatgcaagg caacatgtgt agatctcttg tcttattctt ttgtctataa tactgtattg 120  
ngtagtccaa gctctcgna gtccagccac tngaaacat gctcccttta gattaacctc 180  
gtggacnctn ttgttgnatt gtctgaactg tagngccctg tatcttgctt ctgtctgmga 240  
attctgttgc ttctggggca tttccttgng atgcagagga ccaccacaca gatgacagca 300  
atctgaattg ntccaatcac agctgcgatt aagacatact gaaatcgtag aggaccggga 360  
acaacgtata gaacactgga gtccttt 387



<210> 433  
<211> 281  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(281)  
<223> n = A,T,C or G

<400> 433  
ttcaactagc anagaanact gcttcagggn gtgtaaaatg aaaggcttcc acgcagttat 60  
ctgattaaag aacactaaga gagggacaag gctagaagcc gcaggatgtc tacactatag 120  
caggcnctat ttgggttggc tggaggagct gtggaaaaca tggagagatt ggcgctggag 180  
atcgccgtgg ctattcctcn ttgntattac accagngagg ntctctgtnt gccactgggt 240  
tnnaaaaccg ntatacaata atgatagaat aggacacaca t 281

<210> 434  
<211> 484  
<212> DNA  
<213> Homo sapiens

<400> 434  
ttttaaaata agcatttagt gctcagtcce tactgagtag tctttctctc cctcctctgt 60  
aattttaattc tttcaacttg caatttgcaa ggattacaca tttcactgtg atgtatatgt 120  
tgttgcaaaa aaaaaaaagt gtctttgttt aaaattactt ggtttgtgaa tccatcttgc 180  
tttttcccca ttggaactag tcattaaccc atctctgaac tggtagaaaa acatctgaag 240  
agctagtcta tcagcatctg acaggtgaat tggatgggtc tcagaacccat ttcaccaga 300  
cagcctgttt ctatcctgtt taataaatta gtttgggttc totacatgca taacaaaccc 360  
tgcaccaatc tgtcacataa aagtctgtga cttgaagttt agtcagcacc cccaccaaac 420  
tttatttttc tatgtgtttt ttgcaacata tgagtgtttt gaaaataaag taccatgtc 480  
ttaa 484

<210> 435  
<211> 424  
<212> DNA  
<213> Homo sapiens

<400> 435  
gcgcccgtca gaggaggta ctttctgcct tccacgtcct ccttcaagga agccccatgt 60  
gggtagcttt caatatcgca ggttcttact cctctgcctc tataagctca aaccaccaa 120  
cgatcgggca agtaaaccce ctccctcgcc gacttcggaa ctggcgagag ttcagcgag 180  
atgggcctgt ggggaggggg caagatagat gagggggagc ggcatggtgc ggggtgaccc 240  
cttgagagaga ggaaaaaggc cacaagaggg gctgccaccg ccaactaacg agatggccct 300  
ggtagagacc tttgggggtc tggaacctct ggactcccca tgctctaact cccacactct 360  
gctatcagaa acttaaacctt gaggattttc tctgtttttc actcgcaata aattcagagc 420  
aaac 424

<210> 436  
<211> 667  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(667)  
<223> n = A,T,C or G

&lt;400&gt; 436

```
accttgaggaa nactctcaca atataaaggg tcgtagactt tactccaaat tccaaaaagg 60
tcctggccat gtaatcctga aagttttccc aaggtagcta taaaatcctt ataagggtgc 120
agcctcttct ggaattcctc tgatttcaaa gtctcactct caagttcttg aaaacgaggg 180
cagttcctga aaggcaggta tagcaactga tcttcagaaa gaggaactgt gtgcaccggg 240
atgggctgcc agagtaggat aggattccag atgctgacac cttctggggg aaacaggggt 300
gccaggtttg tcatagcact catcaaagtc cgggtcaacgt ctgtgcttcg aatataaacc 360
tgttcatggt tataggactc attcaagaat tttctatatc tctttcttat atactctcca 420
agttcataat gctgctccat gccagctgg gtgagttggc caaatccttg tggccatgag 480
gattccttta tggggtcagt gggaaagggt tcaatgggac ttcggtctcc atgccgaaac 540
accaaagtc caaacttcaa ctcttgggt agtacacttc ggtctagcca gaaaaaagc 600
agaaacaaga agccaaggct aaggcttgct gcctgcccag gagggagggt gcagctctca 660
tgttgag 667
```

&lt;210&gt; 437

&lt;211&gt; 693

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 437

```
ctacgtctca accctcattt ttaggtaagg aatcttaagt ccaaagatat taagtgactc 60
acacagccag gtaaggaaag ctggattggc aactaggac tctaccatac cgggttttgt 120
taaagctcag gttaggaggc tgataagctt ggaaggaaact tcagacagct ttttcagatc 180
ataaaagata attcttagcc catgttcttc tccagagcag acctgaaatg acagcacagc 240
agggtactct ctattttcac cctcttgct tctactctct ggcagtcaga cctgtgggag 300
gccatgggag aaagcagctc tctggatggt tgtacagatc atggactatt ctctgtggac 360
catttctcca ggttacccta ggtgtcacta ttggggggag agccagcatc tttagctttc 420
atgttagttt ctgtctgtct tcagtagagg aaacttttgc tcttcacact tcacatctga 480
acacctaact gctgttgctc ctgaggtggt gaaagacaga tatagagctt acagtattta 540
tcctatttct aggcactgag ggctgtgggg taccttggtg tgccaaaaca gatcctgttt 600
taaggacatg ttgcttcaga gatgtctgta actatctggg ggctctgttg gctctttacc 660
ctgcatcatg tgctctcttg gctgaaaatg acc 693
```

&lt;210&gt; 438

&lt;211&gt; 360

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 438

```
ctgcttatca caatgaatgt tctcctgggc agcgttgtga tctttgccac cttcgtgact 60
ttatgcaatg catcatgcta tttcatacct aatgagggag ttccaggaga ttcaaccagg 120
atgtttctac acctgtgggt tatgacaaag acaactgcc aagaatcttc aagaaggagg 180
actgcaagta tatctggtgg agaagaagga cccaaaaaag acctgttctg tcagtgaatg 240
gataatctaa tgtgcttcta gtaggcacag ggctcccagg ccaggcctca ttctcctctg 300
gcctctaata gtcaataatt gtgtagccat gcctatcagt aaaaagattt ttgagcaaac 360
```

&lt;210&gt; 439

&lt;211&gt; 431

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(431)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 439

```
gttcctnnta actcctgcc aaacacagctc tcctcaacat gagagctgca cccctcctcc 60
```

```

tggccagggc agcaagcctt agccttggct tcttgtttct gcttttttcc tggctagacc 120
gaagtgtact agccaaggag ttgaagtttg tgacttttgg gtttcggcat ggagaccgaa 180
gtcccattga cacctttccc actgacccca taaaggaatc ctcatggcca caaggatttg 240
gccaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataagaaaga 300
gatatagaaa attcttgaat gagtccata aacatgaaca ggtttatatt cgaagcacag 360
acgttgaccg gactttgatg agtgctatga caaacctggc agcccgtcga cgcggccgcg 420
aatttagtag t                                     431

```

&lt;210&gt; 440

&lt;211&gt; 523

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 440

```

agagataaag cttaggtcaa agttcataga gttcccatga actatatgac tggccacaca 60
ggatcttttg tatttaagga ttctgagatt ttgcttgagc aggattagat aaggctgttc 120
tttaaatgtc tgaaatggaa cagatttcaa aaaaaaaccc cacaatctag ggtgggaaca 180
aggaaggaaa gatgtgaata ggctgatggg caaaaaacca atttaccocat cagttccagc 240
cttctctcaa ggagaggcaa agaaaggaga tacagtggag acatctggaa agttttctcc 300
actggaaaac tgctactatc tgtttttata tttctgttaa aatatatgag gctacagaac 360
taaaaattaa aacctctttg tgtcccttgg tcctggaaca tttatgttcc ttttaaagaa 420
acaaaaatca aactttacag aaagatttga tgtatgtaat acatatagca gctcttgaag 480
tatatatatc atagcaaata agtcactctga tgagaacaag cta                                     523

```

&lt;210&gt; 441

&lt;211&gt; 430

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 441

```

gttcctccta actcctgcca gaaacagctc tcctcaacat gagagctgca cccctcctcc 60
tggccagggc agcaagcctt agccttggct tcttgtttct gcttttttcc tggctagacc 120
gaagtgtact agccaaggag ttgaagtttg tgacttttgg gtttcggcat ggagaccgaa 180
gtcccattga cacctttccc actgacccca taaaggaatc ctcatggcca caaggatttg 240
gccaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataagaaaga 300
gatatagaaa attcttgaat gagtccata aacatgaaca ggtttatatt cgaagcacag 360
acgttgaccg gactttgatg agtgctatga caaacctggc agcccgtcga cgcggccgcg 420
aatttagtag                                     430

```

&lt;210&gt; 442

&lt;211&gt; 362

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 442

```

ctaaggaatt agtagtggtc ccatcacttg tttggagtgt gctattctaa aagattttga 60
tttcttgtaa tgacaattat attttaactt tgggtgggga aagagttata ggaccacagt 120
cttcacttct gatacttgta aattaatctt ttattgcact tgttttgacc attaaagctat 180
atgttttagaa atggtcattt tacggaaaaa ttagaaaaat tctgataata gtgcagaata 240
aatgaattaa tgttttactt aatttatatt gaactgtcaa tgacaaataa aaattctttt 300
tgattatttt ttgttttcat ttaccagaat aaaaactaag aattaaaagt ttgattacag 360
tc                                     362

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&lt;210&gt; 443

&lt;211&gt; 624

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(624)  
 <223> n = A,T,C or G

<400> 443  
 tttttttttt gcaacacaaat atacatcaca gtgaaatgtg taatccttgc aaattgcaag 60  
 ttgaaagaat taaattcaga ggaggggaga gaaagagtag tcagtaggga ctgagcacta 120  
 aatgcttatt ttaaaagaaa tgtaaagagc agaaagcaat tcaggctacc ctgccttttg 180  
 tgctggctag tactccggtc ggtgtcagca gcacgtggca ttgaacattg caatgtggag 240  
 cccaaaccac agaaaatggg gtgaaattgg ccaactttct attaaacttg cttcctgttt 300  
 tataaaatat tgtgaataat atcacctact tcaaagggca gttatgaggc ttaaatgaac 360  
 taacgcctac aaaacactta aacatagata acataggtgc aagtactatg tatctggtac 420  
 atggtaaaaca tccttattat taaagtcaac gctaaaatga atgtgtgtgc atatgctaata 480  
 agtacagaga gagggcactt aaaccaacta agggcctgga gggaagggtt cctggaaaaga 540  
 ngatgcttgt gctgggtcca aatcttggtc tactatgacc ttggccaaat tatttaaact 600  
 ttgtccctat ctgctaaaca gatc 624

<210> 444  
 <211> 425  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(425)  
 <223> n = A,T,C or G

<400> 444  
 gcacatcatt nntcttgcatt tctttgagaa taagaagatc agtaaatagt tcagaagtgg 60  
 gaagctttgt ccaggcctgt gtgtgaaccc aatgttttgc ttagaaatag aacaagtaag 120  
 ttcattgcta tagcataaca caaaatttgc ataagtgggtg gtcagcaaat ccttgaatgc 180  
 tgcttaatgt gagaggttgg taaaatcctt tgtgcaacac tctaactccc tgaatgtttt 240  
 gctgtgctgg gacctgtgca tgccagacaa ggccaagctg gctgaaagag caaccagcca 300  
 cctctgcaat ctgccacctc ctgctggcag gatttgtttt tgcactcctg gaagagccaa 360  
 ggaggcacca gggcataagt gagtagactt atggtcgacg cggccgcgaa tttagtagta 420  
 gtaga 425

<210> 445  
 <211> 414  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(414)  
 <223> n = A,T,C or G

<400> 445  
 catgtttatg nttttggatt actttgggca cctagtgttt ctaaatoctc tatcattcctt 60  
 ttctgttttt caaaagcaga gatggccaga gtctcaacaa actgtatcct caagtctttg 120  
 tgaaattcct tgcattgtggc agattatttg atgtagtctt cttaactag catataaatc 180  
 tgggtgtgtt cagataaatg aacagcaaaa tgtggtggaa ttaccatttg gaacattgtg 240  
 aatgaaaaat tgtgtctcta gattatgtaa caaataacta tttcctaacc attgatcttt 300  
 ggatttttat aatcctactc acaaatgact aggcctctcc tcttgtaatt tgaagcagtg 360  
 tgggtgctgg attgataaaa aaaaaaaaag tcgacgcggc cgcgaattta gtag 414

<210> 446

<211> 631  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(631)  
 <223> n = A,T,C or G

<400> 446  
 acaaattaga anaaagtgcc agagaacacc acataccttg tccggaacat tacaatggct 60  
 tctgcatgca tgggaagtgt gagcattcta tcaatatgca ggagccatct tgcaggtgtg 120  
 atgctggtta tactggacaa cactgtgaaa aaaaggacta cagtgttcta tacgttgttc 180  
 ccggtcctgt acgatttcag tatgtcttaa tcgcagctgt gattggaaca attcagattg 240  
 ctgtcatctg tgtggtggtc ctctgcatca caagggccaa actttaggta atagcattgg 300  
 actgagattt gtaaaactttc caaccttcca ggaaatgccc cagaagcaac agaattcaca 360  
 gacagaagca aaatacaggg cactacagtt cagacaatac aacaagagcg tccacgaggt 420  
 taatctaaag ggagcatggt tcacagtggtc tggactaccg agagcttggga ctacacaata 480  
 cagtattata gacaaaagaa taagacaaga gatctacaca tgttgccctg catttgtgtg 540  
 aatctacacc aatgaaaaca tgtactacag ctatatattga ttatgtatgg atatatttga 600  
 aatagtatac attgtcttga tgttttttct g 631

<210> 447  
 <211> 585  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(585)  
 <223> n = A,T,C or G

<400> 447  
 ccttgggaaa antntcacia tataaagggt cgtagacttt actccaaatt ccaaaaaggt 60  
 cctggccatg taatcctgaa agttttccca aggtagctat aaaatcctta taagggtgca 120  
 gcctcttctg gaattcctct gatttcaaag tctcactctc aagticttga aaacgagggc 180  
 agttcctgaa aggcaggtat agcaactgat cttcagaaag aggaactgtg tgcaccggga 240  
 tgggctgcca gagtaggata ggattccaga tgctgacacc ttctggggga aacagggctg 300  
 ccaggtttgt catagcactc atcaaagtcc ggtcaacgtc tgtgcttcga atataaacct 360  
 gttcatgttt ataggactca ttcaagaatt ttctatatct ctttcttata tactctccaa 420  
 gttcataatg ctgctccatg ccagctggg tgagttggcc aaatccttgt ggccatgagg 480  
 attcctttat ggggtcagtg ggaaagggtg caatgggact tcggtctcca tgccgaaaca 540  
 ccaaagtcac aaacttcaac tccttggcta gtacacttcg gtcta 585

<210> 448  
 <211> 93  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(93)  
 <223> n = A,T,C or G

<400> 448  
 tgctcgtggg tcattctgan ncccgaactg accntgccag ccctgccgan gggccnccat 60  
 ggctccctag tgccctggag agganggggc tag 93

<210> 449  
 <211> 706  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(706)  
 <223> n = A,T,C or G

<400> 449  
 ccaagttcat gctntgtgct ggacgctgga cagggggcaa aagcnnttgc tcgtgggtca 60  
 ttctganecac cgaactgacc atgccagccc tgccgatggt cctccatggc tccctagtgc 120  
 cctggagagg aggtgtctag tcagagagta gtcctggaag gtggcctctg ngaggagcca 180  
 cggggacagc atcctgcaga tggtcgggag cgtoeccattc gccattcagg ctgcgcaact 240  
 gttggaagg gcgatcggtg cgggcctctt cgctattacg ccagctggcg aaagggggat 300  
 gtgctgcaag gcgattaagt tgggtaacgc caggggttttc ccagtncga cgttgtaaaa 360  
 cgacggccag tgaattgaat ttaggtgacn ctatagaaga gctatgacgt cgcattgcacg 420  
 cgtacgtaag ctggatctct ctagagcggc cgcctactac tactaaattc gcggccgcgt 480  
 cgacgtggga tcncactga gagagtggag agtgacatgt gctggacnct gtccatgaag 540  
 cactgagcag aagctggagg cacaacgcnc cagacactca cagctactca ggaggctgag 600  
 aacaggttga acctgggagg tggaggttgc aatgagctga gatcaggccn ctgcncacca 660  
 gcatggatga cagagtgaag ctccatctta aaaaaaaaaa aaaaaa 706

<210> 450  
 <211> 493  
 <212> DNA  
 <213> Homo sapiens

<400> 450  
 gagacggagt gtcactctgt tgcccaggct ggagtgcagc aagacactgt ctaagaaaaa 60  
 acagttttaa aaggtaaaac aacataaaaa gaaatatact atagtggaaa taagagagtc 120  
 aaatgaggct gagaacttta caaagggatc ttacagacat gtgcgaata tcaactgcag 180  
 agcctaagta taagaacaac ctttggggag aaaccatcat ttgacagtga ggtacaattc 240  
 caagtcaagg agtgaaatgg gtggaattaa actcaatta atcctgccag ctgaaacgca 300  
 agagacactg tcagagagtt aaaaagttag ttctatccat gaggtgattc cacagtcttc 360  
 tcaagtcaac acatctgtga actcacagac caagttctta aaccactgtt caaactctgc 420  
 tacacatcag aatcacctgg agagctttac aaactcccat tgccgagggt cgacgcggcc 480  
 gcgaatttag tag 493

<210> 451  
 <211> 501  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <222> (1)...(501)  
 <223> n = A,T,C or G

<400> 451  
 gggcgcgctc cattcgccat tcaggctgag caactgttgg gaagggcgat cgggtcgggc 60  
 ctcttcgcta ttacgccagc tggcgaaagg gggatgtgct gcaaggcgat taagttgggt 120  
 aacgccaggg ttttccagct cncgacgttg taaaacgacg gccagtgaat tgaatttagg 180  
 tgacnctata gaagagctat gacgtcgcat gcacgcgtac gtaagcttgg atcctctaga 240  
 gggcgcgct actactacta aattcgcgcc cgcgtcgacg tgggatccnc actgagagag 300  
 tggagagtga catgtgctgg acnctgtcca tgaagcactg agcagaagct ggaggcacia 360  
 cgcncacagc actcacagct actcaggagg ctgagaacag gttgaacctg ggaggtggag 420

gttgcaatga gctgagatca ggccnctgcn ccccgatg gatgacagag tgaaactcca 480  
tcttaaaaaa aaaaaaaaaa a 501

<210> 452  
<211> 51  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(51)  
<223> n = A,T,C or G

<400> 452  
agacggtttc accnttacaa cnccttttag gatgggnntt ggggagcaag c 51

<210> 453  
<211> 317  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...(317)  
<223> n = A,T,C or G

<400> 453  
tacctcttgc tttttcccca ttggaactag tcattaaccc atctctgaac tggtagaaaa 60  
acatctgaag agctagtcta tcagcatctg gcaagtgaat tggatgggtc tcagaaccat 120  
ttcacccana cagcctgttt ctatcctgtt taataaatta gtttgggtc tctacatgca 180  
taacaaaccc tgctccaatc tgtcacataa aagtctgtga cttgaagttt antcagcacc 240  
cccacaaac tttattttc tatgtgtttt ttgcaacata tgagtgtttt gaaaataagg 300  
taccatgtc tttatta 317

<210> 454  
<211> 231  
<212> DNA  
<213> Homo sapiens

<400> 454  
ttcgaggtag aatcaactct cagagtgtag tttccttcta tagatgagtc agcattaata 60  
taagccacgc cagctcttg aaggagtctt gaattctcct ctgctcactc agtagaacca 120  
agaagaccaa attcttctgc atcccagctt gcaaacaaaa ttgttcttct aggtctccac 180  
ccttcctttt tcagtgttcc aaagctcctc acaatttcat gaacaacagc t 231

<210> 455  
<211> 231  
<212> DNA  
<213> Homo sapiens

<400> 455  
taccaaagag ggcataataa tcagtctcac agtaggggtc accatcctcc aagtgaaaaa 60  
cattgttccg aatgggcttt ccacaggcta cacacacaaa acaggaaaca tgccaagttt 120  
gtttcaacgc attgatgact tctccaagga tcttcctttg gcacagacca cattcagggg 180  
caaagaattt ctcatagcac agctcacaat acagggtctc tttctcctct a 231

<210> 456  
<211> 231

<212> DNA

<213> Homo sapiens

<400> 456

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ttggcaggta cccttcaaaa gaagacacca taccttatgc gttattaggt ggaataatca 60
ttccattcag tattatcggtt attattcttg gagaaacct gtctgtttac tgtaaccttt 120
tgcactcaaa ttcctttatc aggaataact acatagccac tatttacaaa gccattggaa 180
cctttttatt tgggtgcagct gctagtcagt cctgactga cattgccaag t 231
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<210> 457

<211> 231

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_feature

<222> (1)...(231)

<223> n = A,T,C or G

<400> 457

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cgaggtagcc aggggtctga aaatctctnn ttantagtc gatagcaaaa ttgttcatca 60
gcattcctta atatgatctt gctataatta gatttttctc cattagagtt catacagttt 120
tatttgattt tattagcaat ctctttcaga agacccttga gatcattaag ctttgtatcc 180
agttgtctaa atcgatgcct catttcctct gaggtgtcgc tggcttttgt g 231
```

<210> 458

<211> 231

<212> DNA

<213> Homo sapiens

<400> 458

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aggtctgggt cccccactt ccactccct ctactctctc taggactggg ctgggccaaag 60
agaagagggg tggtaggga agccgttgag acctgaagcc ccacctcta cttccttca 120
acacctaac cttgggtaac agcatttgga attatcattt gggatgagta gaatttccaa 180
ggtcctgggt taggcatttt ggggggccag accccaggag aagaagattc t 231
```

<210> 459

<211> 231

<212> DNA

<213> Homo sapiens

<400> 459

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ggtaccgagg ctgctgaca cagagaaacc ccaacgcgag gaaaggaatg gccagccaca 60
ccttcgcgaa acctgtggtg gccaccagt cctaacggga caggacagag agacagagca 120
gccctgact gttttccctc caccacagcc atcctgtccc tcattggctc tgtgctttcc 180
actatacaca gtcaccgtcc caatgagaaa caagaaggag caccctccac a 231
```

<210> 460

<211> 231

<212> DNA

<213> Homo sapiens

<400> 460

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gcaggataaa catgctgcaa caacagatgt gactaggaac ggccgggtgac atggggaggg 60
cctatcaccc tattcttggg ggctgcttct tcacagtgat catgaagcct agcagcaaat 120
cccacctccc cacacgcaca cgccagcct ggagcccaca gaagggtcct cctgcagcca 180
gtggagcttg gtccagcctc cagtcacccc ctaccaggct taaggataga a 231
```



<210> 461  
<211> 231  
<212> DNA  
<213> Homo sapiens

<400> 461  
cgaggtttga gaagctctaa tgtgcagggg agccgagaag caggcggcct agggagggtc 60  
gcgtgtgctc cagaagagtg tgtgcatgcc agaggggaaa caggcgcctg tgtgtcctgg 120  
gtggggttca gtgaggagtg ggaaattggt tcagcagaaac caagccgttg ggtgaataag 180  
agggggattc catggcactg atagagccct atagtttcag agctgggaat t 231

<210> 462  
<211> 231  
<212> DNA  
<213> Homo sapiens

<400> 462  
aggtaccctc attgtagcca tgggaaaatt gatgttcagt ggggatcagt gaattaaatg 60  
gggtcatgca agtataaaaa ttaaaaaaaa aagacttcat gcccaatctc atatgatgtg 120  
gaagaactgt tagagagacc aacagggtag tgggttagag atttccagag tcttacattt 180  
tctagaggag gtatttaatt tcttctcact catccagtgt tgtatttagg a 231

<210> 463  
<211> 231  
<212> DNA  
<213> Homo sapiens

<400> 463  
tactccagcc tggtagacaga gcgagaccct atcaccgccc cccacccccc caaaaaaaaa 60  
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catttgacag gtgtcttttc ctctggacct cggtgtcccc atctgagtga gaaaaggcag 180  
tggggagggtg gatcttccag tcgaagcggt atagaagccc gtgtgaaaag c 231

<210> 464  
<211> 231  
<212> DNA  
<213> Homo sapiens

<400> 464  
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cctgcttcag tgactgtgtg cctgtagtcc cagctactcg ggagtctgtg tgaggccagg 180  
ggtgccagcg caccagctag atgctctgta acttctaggg cccattttcc c 231

<210> 465  
<211> 231  
<212> DNA  
<213> Homo sapiens

<400> 465  
catgttggtg tagctgtggt aatgctggct gcacttcaga cagggttaac ttcagctcct 60  
gtggcaaat agcaacaaat tctgacatca tatttatggt ttctgtatct ttgttgatga 120  
aggatggcac aatttttgct tgtgttcata atatactcag attagtccag ctccatcaga 180  
taaactggag acatgcagga cattagggtg gtgtgttagc tctggtaatg a 231

<210> 466  
<211> 231  
<212> DNA

<213> Homo sapiens

<400> 466

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caggtagctc tttccattgg atactgtgct agcaagcatg ctctccgggg tttttttaat 60
ggccttcgaa cagaacttgc cacataccca ggtataatag tttctaacat ttgccagga 120
cctgtgcaat caaatattgt ggagaattcc ctgactggag aagtcacaaa gactatagga 180
aataatggag accagtccca caagatgaca accagtcgtt gtgtgcggct g          231
```

<210> 467

<211> 311

<212> DNA

<213> Homo sapiens

<400> 467

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tggtggtttt tctccttttt catcaagact cctcagcagg gagcccagac cagcctgcac 120
tgtgccttaa cagaaggtct tgagattcta agtgggaatc atttcagtga ctgtcatgtg 180
gcatgggtct tggcccaagc tcgtaatgag actatagcaa ggcggctgtg ggacgtcagt 240
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ctgcagcaga c          311
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<210> 468

<211> 3112

<212> DNA

<213> Homo sapiens

<400> 468

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&lt;210&gt; 469

&lt;211&gt; 2229

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 469

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&lt;210&gt; 470

&lt;211&gt; 2426

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 470

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&lt;211&gt; 1594

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 474

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ccctccatca aactgcca cccaggttg gggctacccc agcccatctt taaaaacag 1260
ggcaaggtga actaatggag tgggtggagg agttggaaga aatcccagcg tcagtcaccg 1320

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ggatagaatt cccaaggaac cctctttttg gaggatggtt tccatttctg gaggcgatct 1380
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ggtgggaaga gtgtggctgt gtactttgaa ctctgtgaaa ttctctgact catgtccaca 1500
aaaccaacag ttttgtgaat gtgtctggag gcaagggaag ggccactcag gatctatggt 1560
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<210> 475
<211> 2414
<212> DNA
<213> Homo sapiens

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<220>
<221> unsure
<222> (33)
<223> n=A,T,C or G

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<400> 475
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agctaattat tcatgctgaa cacattttta atgctgtaaa ttagataat gtaatttatg 180
tattcattat gcctctttag tagtttagag aaaacgtcaa aagaaatggc cccagaataa 240
gcttcttgat ttgtaaaatt ctatgtcatt ggctcaaatt tgtatagat ctcaaaatat 300
aaatataatg acatctcaga taatatattt gaaatagcaa attcctgtta gaaaataata 360
gtacttaact agatgagaat aacaggctgc cattatttga attgtctcct attcgttttt 420
catttgttgt gttactcatg ttttacttat ggggggatat atataacttc cgctgttttc 480
agaagtattg tatgcagtca gtatgagaat gcaatttaag ttccttgat gctttttcac 540
acttctatta ctagaaataa gaatacagta atattggcaa agaaaattga ccagttcaat 600
aaaatttttt agtaaatctg attgaaaata aacattgctt atggctttct tacatcaata 660
ttgttatgtc ctagacacct tatctgaaat tacggcttca aaattctaata tatgtgcaaa 720
tgtgtaaaat atcaatactt tatgttcaag ctggggcctc ttcaggcgctc ctgggctgag 780
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ccatgtggac acaaggacac acagacactg tcacacagat acacaaaaca ctgtcacacg 1260
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ttttctactc actttttcct gcctatccc ccatctcttc cacaggtaac cactgatcca 2040
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tcctctcca tccaggacct gaggggtgtc cttttctgog cttccttggg tggcagtcct 2340
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<210> 476  
<211> 3434  
<212> DNA  
<213> Homo sapiens

<400> 476

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tgccaagagg cagaccacag gtcatcttga ggaggacttt atgttccagt ccagaaagca 180
gccagtggta ccaccaggg gacttgtgct tctgtggccc aggccagacg tagaatttga 240
caaagtacag acggtctcag tcagagcagc atgtcgggtcc ccggggcctg tgcattgccg 300
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ctgagtggct gccacctgat ggctgatgga gcagaggcct gaggaaaagc agatggcact 480
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&lt;210&gt; 477

&lt;211&gt; 140

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 477

Met Asp Gly His Thr Asp Ile Trp Arg Asn His Met Asp Thr Pro Pro  
                                   5                                  10                                  15

His Tyr His Arg Asp Thr Asp Thr Arg Arg His His His Met Asp Thr  
                                   20                                  25                                  30

Leu Ser His Tyr His Arg Asp Thr Arg His His Thr Val Thr Trp Thr  
                                   35                                  40                                  45

His His His Thr His Glu His Thr Asp Thr Leu Pro Tyr Gly His Trp  
                                   50                                  55                                  60

His Thr His Cys His Thr Val Thr Trp Thr His Leu His Thr Ile Thr  
                                   65                                  70                                  75                                  80

Pro Pro His Thr Leu Pro Val Asp Thr Arg Thr His Arg His Cys His  
                                   85                                  90                                  95

Thr Asp Thr Gln Asn Thr Val Thr Arg Arg His His His Ala Asp Thr  
                                   100                                  105                                  110

Pro Pro Leu Trp Cys Arg Leu Asn Tyr Pro Ala Gly Gly Thr Ala Val  
                                   115                                  120                                  125

Ala Tyr Ser Cys Leu Ser Asp Trp Leu Ser Pro Gln  
                                   130                                  135                                  140

&lt;210&gt; 478

&lt;211&gt; 143

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 478

Met Tyr Arg His Thr Glu Thr Leu Pro His Gly Asp Thr Val Thr Gln  
                                   5                                  10                                  15

Ser His Gly His Thr Gly Ile Val Thr Trp Thr Asp Thr Gln Thr Tyr  
                                   20                                  25                                  30

Gly Glu Ile Thr Trp Thr His His His Thr Ile Thr Gly Thr Gln Thr  
                                   35                                  40                                  45

His Gly Asp Ile Thr Thr Trp Thr His Cys His Thr Thr Thr Gly Thr

166.

50                      55                      60  
 Arg Asp Ile Thr Leu Ser His Gly His Thr Ile Thr His Met Asn Thr  
 65                      70                      75                      80  
 Pro Thr His Cys His Met Asp Thr Gly Thr His Thr Ala Thr Leu Ser  
 85                      90                      95  
 His Gly His Thr Ser Thr Pro Ser His His His Thr His Cys Leu Trp  
 100                      105                      110  
 Thr Gln Gly His Thr Asp Thr Val Thr Gln Ile His Lys Thr Leu Ser  
 115                      120                      125  
 His Gly Asp Ile Thr Met Gln Ile His His His Ser Gly Ala Val  
 130                      135                      140  
  
 <210> 479  
 <211> 222  
 <212> PRT  
 <213> Homo sapiens  
  
 <400> 479  
 Met Tyr Arg His Thr Glu Thr Leu Pro His Gly Asp Thr Val Thr Gln  
 5                      10                      15  
 Ser His Glu His Thr Gly Ile Val Thr Trp Thr Asp Thr Gln Thr Tyr  
 20                      25                      30  
 Gly Glu Ile Thr Leu Thr His His His Thr Ile Thr Gly Thr Gln Thr  
 35                      40                      45  
 His Gly Asp Ile Thr Thr Trp Thr His Cys His Thr Thr Thr Gly Thr  
 50                      55                      60  
 Arg Asp Ile Thr Leu Ser His Gly His Thr Ile Thr His Met Asn Thr  
 65                      70                      75                      80  
 Pro Thr His Cys His Met Asp Thr Ala Thr His Thr Ala Thr Leu Ser  
 85                      90                      95  
 His Gly His Thr Ser Ile Pro Ser His His His Thr His Cys His Val  
 100                      105                      110  
 Asp Thr Arg Thr His Arg His Cys His Thr Asp Thr Gln Asn Thr Val  
 115                      120                      125  
 Thr Arg Arg His His His Ala Asp Thr Pro Pro His Gly His Ser Thr  
 130                      135                      140  
 Arg His Ser Ala Thr Gln Ile His His His Thr Glu Met Arg Thr His  
 145                      150                      155                      160  
 Cys His Thr Asp Thr Thr Thr Ser Leu Pro His Phe His Val Ser Ala  
 165                      170                      175  
 Gly Gly Val Gly Pro Thr Thr Leu Gly Ser Asn Arg Glu Ile Thr Trp

167

180 185 190  
 Thr Tyr Ser Glu Gly Lys Ile Phe Phe Tyr Phe Leu Gly Asn Gln Ala  
 195 200 205  
 Arg Leu Cys Leu Lys Lys Arg Lys Lys Lys Gln Tyr Thr Val  
 210 215 220

<210> 480  
 <211> 144  
 <212> PRT  
 <213> Homo sapiens

<400> 480  
 Met Glu Pro Tyr Arg Gly Asn Glu Gln Pro Ser Gln Glu Gln Gly Val  
 5 10 15  
 Cys Cys Leu Trp Gly Leu Gln Ser Leu Pro Gln Gly Ser Tyr Val Thr  
 20 25 30  
 Val Gly Phe Leu Val Val Lys Arg Gln Thr Ile Gly Arg Leu Glu Arg  
 35 40 45  
 Asp Phe Met Phe Lys Cys Arg Lys Gln Pro Gly Leu Pro Pro Ser Gly  
 50 55 60  
 Leu Cys Leu Leu Trp Pro Trp Pro Asn Leu Glu Phe Gly Arg Arg Gln  
 65 70 75 80  
 Asp Arg Leu Thr Trp Ser Ser Val Ser Val Ala Gly Val Cys Ala Cys  
 85 90 95  
 Arg Ala Arg Pro Gly Trp Leu Gly Glu Gln Pro Ala Thr Ser Ala Gly  
 100 105 110  
 Val Arg Leu Glu Gln Val Glu Gln Pro Pro Ala His Pro Leu Gln Glu  
 115 120 125  
 Ala Gly Val Ala Arg Phe Pro Arg Pro Glu Trp Val Pro Pro Asn Gly  
 130 135 140

<210> 481  
 <211> 167  
 <212> PRT  
 <213> Homo sapiens

<400> 481  
 Met His Gly Pro Gln Val Leu Ala Arg Cys Ser Glu Cys Ala Cys Pro  
 5 10 15  
 Ala Leu Ala Ala Thr Ser Ala Gly Val Arg Leu Glu Gly Val Asp Arg  
 20 25 30

Pro	Pro	Thr	Leu	Pro	Ser	Gln	Gly	Ser	Gly	Trp	Pro	Cys	Ser	His	Ser	
35				40				45								
Leu	Ser	Gly	Cys	His	Leu	Met	Ala	Asp	Gly	Ala	Lys	Ala	Leu	Gly	Lys	
50				55				60								
Ala	Asp	Gly	Pro	Trp	Pro	Tyr	Leu	Phe	Val	Arg	Arg	Thr	Asp	Val	Pro	
65				70				75				80				
Cys	Pro	Ala	Ala	Ser	Glu	Val	Gly	Gly	Cys	Ala	Pro	Ser	Ser	Trp	Arg	
				85				90				95				
Ala	Leu	Ala	Glu	Val	Thr	Gly	Cys	Ser	Leu	Gly	Pro	Leu	Gly	Leu	Ala	
				100				105				110				
Gln	His	Ala	Gln	Ala	Ser	Val	Leu	Leu	Leu	Cys	Tyr	Lys	Trp	Ser	His	
115				120				125								
Ile	Gly	Glu	Thr	Ser	Ser	His	Leu	Arg	Ser	Lys	Val	Tyr	Ala	Ala	Phe	
130				135				140								
Gly	Gly	Ser	Ser	Pro	Cys	Leu	Lys	Gly	Leu	Met	Ser	Leu	Trp	Ala	Ser	
145				150				155				160				
Trp	Leu	Ser	Arg	Gly	Arg	Pro										
				165												

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<210> 482
<211> 143
<212> PRT
<213> Homo sapiens
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<400> 482

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Pro	Cys	Leu	Trp	Gly	Ser	Ser	Pro	Cys	Leu	Arg	Cys	His	Met	Ala	Leu
			20					25					30		
Arg	Ala	Ser	Trp	Leu	Pro	Gly	Gly	Gly	Pro	Gln	Ala	Ile	Leu	Gly	Arg
		35				40						45			
Thr	Leu	Cys	Ser	Ser	Ala	Glu	Ser	Ser	Gln	Asp	Cys	His	Pro	Gly	Gly
	50					55					60				
Pro	Ser	Ile	Ala	Leu	Ala	Lys	Pro	Cys	Arg	Gly	Val	Trp	Leu	Leu	Phe
65					70					75					80
Glu	Pro	Ala	Trp	Pro	Pro	Trp	His	Ala	Arg	Ala	Pro	Gly	Ala	Gly	Thr
				85					90					95	
Leu	Leu	Arg	Val	Cys	Leu	Ser	Cys	Leu	Gly	Cys	His	Leu	Cys	Gly	Gly
			100					105					110		
Ala	Ser	Gly	Gly	Gly	Gly	Pro	Ala	Thr	Asn	Leu	Thr	Gln	Ser	Arg	Lys
		115					120					125			

169

Trp Met Ala Met Phe Pro Gln Pro Glu Trp Leu Pro Pro Asp Gly  
 130 135 140

<210> 483  
 <211> 143  
 <212> PRT  
 <213> Homo sapiens

<400> 483  
 Met Glu Thr Gln Arg Gly Asn Lys Gln Arg Ala Gln Glu Gln Gly Val  
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 Cys Cys Leu Trp Gly Ser Ser Pro Cys Leu Gly Ser Tyr Gly Thr Ala  
 20 25 30  
 Gly Phe Leu Val Ala Lys Arg Arg Thr Thr Gly Leu Leu Glu Glu Asp  
 35 40 45  
 Phe Thr Phe Lys Cys Arg Lys Gln Pro Lys Leu Pro Ser Met Arg Leu  
 50 55 60  
 Ser Leu Leu Trp Pro Trp Arg Asp Leu Lys Phe Val Pro Arg Gln Asp  
 65 70 75 80  
 Lys Leu Thr Arg Ser Ser Val Ser Val Ala Gly Ala Tyr Ala Cys Arg  
 85 90 95  
 Ala Gly Pro Gly Trp Leu Lys Glu Gln Pro Ala Thr Ser Ala Arg Val  
 100 105 110  
 Arg Leu Val Gln Ala Glu His Pro Pro Pro His Pro Leu Glu Glu Val  
 115 120 125  
 Gly Met Ala Arg Phe Pro Gln Pro Glu Cys Leu Pro Pro Tyr Cys  
 130 135 140

<210> 484  
 <211> 30  
 <212> PRT  
 <213> Homo Sapien

<400> 484  
 Thr Ala Ala Ser Asp Asn Phe Gln Leu Ser Gln Gly Gly Gln Gly Phe  
 1 5 10 15  
 Ala Ile Pro Ile Gly Gln Ala Met Ala Ile Ala Gly Gln Ile  
 20 25 30

<210> 485  
 <211> 31  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 485  
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<210> 486  
<211> 27  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Made in a lab

<400> 486  
gcgaattctc acgctgagta tttggcc 27

<210> 487  
<211> 36  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Made in a lab

<400> 487  
cccgaattct tagctgccca tccgaacgcc ttcac 36

<210> 488  
<211> 33  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Made in a lab

<400> 488  
gggaagcttc ttccccggct gcaccagctg tgc 33

<210> 489  
<211> 19  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Made in a lab

<400> 489  
Met Asp Arg Leu Val Gln Arg Phe Gly Thr Arg Ala Val Tyr Leu Ala  
1 5 10 15  
Ser Val Ala

<210> 490  
<211> 20  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Made in a lab

<400> 490  
Tyr Leu Ala Ser Val Ala Ala Phe Pro Val Ala Ala Gly Ala Thr Cys

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1
Leu Ser His Ser
20

<210> 491
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 491
Thr Cys Leu Ser His Ser Val Ala Val Val Thr Ala Ser Ala Ala Leu
1 5 10 15
Thr Gly Phe Thr
20

<210> 492
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 492
Ala Leu Thr Gly Phe Thr Phe Ser Ala Leu Gln Ile Leu Pro Tyr Thr
1 5 10 15
Leu Ala Ser Leu
20

<210> 493
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 493
Tyr Thr Leu Ala Ser Leu Tyr His Arg Glu Lys Gln Val Phe Leu Pro
1 5 10 15
Lys Tyr Arg Gly
20

<210> 494
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Made in a lab

<400> 494
Leu Pro Lys Tyr Arg Gly Asp Thr Gly Gly Ala Ser Ser Glu Asp Ser
1 5 10 15
Leu Met Ile Ser

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20

<210> 495  
<211> 20  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Made in a lab

<400> 495  
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1 5 10 15  
Phe Pro Asn Gly  
20

<210> 496  
<211> 21  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Made in a lab

<400> 496  
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Pro Pro Pro Pro Ala  
20

<210> 497  
<211> 20  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Made in a lab

<400> 497  
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<210> 498  
<211> 20  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Made in a lab

<400> 498  
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Val Pro Gly Arg  
20

<210> 499  
 <211> 20  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 499  
 Arg Val Val Pro Gly Arg Gly Ile Cys Leu Asp Leu Ala Ile Leu Asp  
 1 5 10 15  
 Ser Ala Phe Leu  
 20

<210> 500  
 <211> 20  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 500  
 Leu Asp Ser Ala Phe Leu Leu Ser Gln Val Ala Pro Ser Leu Phe Met  
 1 5 10 15  
 Gly Ser Ile Val  
 20

<210> 501  
 <211> 20  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 501  
 Phe Met Gly Ser Ile Val Gln Leu Ser Gln Ser Val Thr Ala Tyr Met  
 1 5 10 15  
 Val Ser Ala Ala  
 20

<210> 502  
 <211> 414  
 <212> DNA  
 <213> Homo Sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(414)  
 <223> n=A,T,C or G

<400> 502  
 caccatggag acaggcctgc gctggctttt cctggctcgt gtgctcaaag gtgtccaatg 60  
 tcagtgggtg gaggagtccg ggggtcgcct ggtcacgcct gggacacctt tgacantcac 120  
 ctgtagagtt tttggaatng acctcagtag caatgcaatg agctgggtcc gccaggctcc 180  
 agggaaaggg ctggaatgga tcggagccat tgataattgt ccacantacg cgacctgggc 240

```

gaaaggccga ttnatnattt ccaaaacctn gaccacgggtg gatttgaaaa tgaccagtcc 300
gacaaccgag gacacggcca cctatntttg tggcagaatg aatactggta atagtgggtg 360
gaagaatatt tggggcccag gcaccctggg caccgtntcc tcagggaac ctaa 414

```

```

<210> 503
<211> 379
<212> DNA
<213> Homo Sapien

```

```

<220>
<221> misc_feature
<222> (1)...(379)
<223> n=A,T,C or G

```

```

<400> 503
atnccgatggt gcttgggtcaa aggtgtccag tgtcagtcgg tggaggagtc cgggggtcgc 60
ctggtcacgc ctgggacacc cctgacactc acctgcaccg tntctggatt ngacatcagt 120
agctatggag tgagctgggt ccgccaggct ccagggaagg ggctggnata catcggtatca 180
ttagtagtag tggtagattt tacgcgagct gggcgaaagg ccgattcacc atttccaaaa 240
cctngaccac ggtggatttg aaaatcacca gtttgacaac cgaggacacg gccacctatt 300
tntgtgccag aggggggttt aattataaag acatttgggg cccaggcacc ctggtcaccg 360
tntccttagg gcaacctaa 379

```

```

<210> 504
<211> 19
<212> PRT
<213> Artificial Sequence

```

```

<220>
<223> Made in a lab

```

```

<400> 504
Gly Phe Thr Asn Tyr Thr Asp Phe Glu Asp Ser Pro Tyr Phe Lys Glu
1 5 10 15
Asn Ser Ala

```

```

<210> 505
<211> 20
<212> PRT
<213> Artificial Sequence

```

```

<220>
<223> Made in a lab

```

```

<400> 505
Lys Glu Asn Ser Ala Phe Pro Pro Phe Cys Cys Asn Asp Asn Val Thr
1 5 10 15
Asn Thr Ala Asn
20

```

```

<210> 506
<211> 407
<212> DNA
<213> Homo Sapien

```

```

<400> 506

```

```

atggagacag gcctgcgctg gcttctcctg gtcgctgcgc tcaaaggtgt ccagtgtcag    60
tcgctggagg agtccggggg tcgcctgggc acgcctggga caccctgac actcacctgc    120
accgtctctg gattctccct cagtagcaat gcaatgatct gggtcggcca ggctccaggg    180
aaggggctgg aatacatcgg atacattagt tatgggtgta gcgcatacta cgcgagctgg    240
gtgaaaggcc gattcaccat ctccaaaacc tcgaccacgg tggatctgag aatgaccagt    300
ctgacaaccg aggacacggc cacctatttc tgtgccagaa atagtgattt tagtggtatg    360
ttgtggggcc caggcacctt ggtcaccgtc tcctcagggc aacctaa                407

```

<210> 507  
 <211> 422  
 <212> DNA  
 <213> Homo Sapien

```

<400> 507
atggagacag gcctgcgctg gcttctcctg gtcgctgtgc tcaaaggtgt ccagtgtcag    60
tcggtggagg agtccggggg tcgcctgggc acgcctggga caccctgac actcacctgt    120
acagtctctg gattctccct cagcaactac gacctgaact gggtcggcca ggctccaggg    180
aaggggctgg aatggatcgg gatcattaat tatgttgta ggacggacta cgcgaactgg    240
gcaaaaggcc gggtcaccat ctccaaaacc tcgaccacgg tggatctcaa gatcgccagt    300
ccgacaaccg aggacacggc cacctatttc tgtgccagag ggtggaagtg cgatgagtct    360
ggctcgtgct tgcgcatctg gggcccaggc accctgggtc ccgtctcctt agggcaacct    420
aa                                422

```

<210> 508  
 <211> 411  
 <212> DNA  
 <213> Homo Sapien

<220>  
 <221> misc\_feature  
 <222> (1)...(411)  
 <223> n=A,T,C or G

```

<400> 508
atggagacag gcctgcgctg cttctcctgg tcgctgtgct caaaggtgtc cagtgtcagt    60
cggtggagga gtccgggggt cgctgggtca cgctggggac accctgaca ctcacctgca    120
cagtctctgg aatcgacctc agtagctact gcatgagctg ggtccggccag gctccagggg    180
aggggctgga atggatcgga atcattggta ctctgggtga cacatactac gcgaggtggg    240
cgaaaggccg attcaccatc tccaaaacct cgaccacggg gcatntgaaa atcnccagtc    300
cgacaaccga ggacacggcc acctatttct gtgccagaga tcttcgggat ggtagtagta    360
ctggttatta taaaatctgg ggcccaggca ccctgggtcac cgtctccttg g                411

```

<210> 509  
 <211> 15  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

```

<400> 509
Leu Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
 1              5              10             15

```

<210> 510  
 <211> 15  
 <212> PRT  
 <213> Artificial Sequence

&lt;220&gt;

&lt;223&gt; Made in a lab

&lt;400&gt; 510

Pro	Glu	Tyr	Asn	Arg	Pro	Leu	Leu	Ala	Asn	Asp	Leu	Met	Leu	Ile
1				5					10					15

&lt;210&gt; 511

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Made in a lab

&lt;400&gt; 511

Tyr	His	Pro	Ser	Met	Phe	Cys	Ala	Gly	Gly	Gly	Gln	Asp	Gln	Lys
1				5					10					15

&lt;210&gt; 512

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Made in a lab

&lt;400&gt; 512

Asp	Ser	Gly	Gly	Pro	Leu	Ile	Cys	Asn	Gly	Tyr	Leu	Gln	Gly	Leu
1				5					10					15

&lt;210&gt; 513

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Made in a lab

&lt;400&gt; 513

Ala	Pro	Cys	Gly	Gln	Val	Gly	Val	Pro	Asx	Val	Tyr	Thr	Asn	Leu
1				5					10					15

&lt;210&gt; 514

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Made in a lab

&lt;400&gt; 514

Leu	Cys	Lys	Phe	Thr	Glu	Trp	Ile	Glu	Lys	Thr	Val	Gln	Ala	Ser
1				5					10					15

&lt;210&gt; 515

<211> 15  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 515  
 Met Val Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg  
 1 5 10 15

<210> 516  
 <211> 15  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 516  
 Val Ser Glu Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln  
 1 5 10 15

<210> 517  
 <211> 15  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 517  
 Glu Val Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met  
 1 5 10 15

<210> 518  
 <211> 15  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 518  
 Arg Ala Glu Pro Gly Thr Glu Ala Arg Arg His Tyr Asp Glu Gly  
 1 5 10 15

<210> 519  
 <211> 17  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 519  
 Arg Ala Glu Pro Gly Thr Glu Ala Arg Arg Asn Tyr Asp Glu Gly Cys  
 1 5 10 15

Gly

<210> 520  
 <211> 25  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 520  
 Val Gly Glu Gly Leu Tyr Gln Gly Val Pro Arg Ala Glu Pro Gly Thr  
 1 5 10 15  
 Glu Ala Arg Arg His Tyr Asp Glu Gly  
 20 25

<210> 521  
 <211> 21  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 521  
 Ala Pro Phe Pro Asn Gly His Val Gly Ala Gly Gly Ser Gly Leu Leu  
 1 5 10 15  
 Pro Pro Pro Pro Ala  
 20

<210> 522  
 <211> 20  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<400> 522  
 Leu Leu Val Val Pro Ala Ile Lys Lys Asp Tyr Gly Ser Gln Glu Asp  
 1 5 10 15  
 Phe Thr Gln Val  
 20

<210> 523  
 <211> 254  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Made in a lab

<220>  
 <221> VARIANT  
 <222> (1)...(254)  
 <223> Xaa = any amino acid

&lt;400&gt; 523

Met Ala Thr Ala Gly Asn Pro Trp Gly Trp Phe Leu Gly Tyr Leu Ile  
 1 5 10 15  
 Leu Gly Val Ala Gly Ser Leu Val Ser Gly Ser Cys Ser Gln Ile Ile  
 20 25 30  
 Asn Gly Glu Asp Cys Ser Pro His Ser Gln Pro Trp Gln Ala Ala Leu  
 35 40 45  
 Val Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln  
 50 55 60  
 Trp Val Leu Ser Ala Thr His Cys Phe Gln Asn Ser Tyr Thr Ile Gly  
 65 70 75 80  
 Leu Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met  
 85 90 95  
 Val Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu  
 100 105 110  
 Leu Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu  
 115 120 125  
 Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala  
 130 135 140  
 Gly Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg  
 145 150 155 160  
 Met Pro Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu Glu  
 165 170 175  
 Val Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys  
 180 185 190  
 Ala Gly Gly Gly Gln Xaa Gln Xaa Asp Ser Cys Asn Gly Asp Ser Gly  
 195 200 205  
 Gly Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly  
 210 215 220  
 Lys Ala Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn Leu  
 225 230 235 240  
 Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser  
 245 250

&lt;210&gt; 524

&lt;211&gt; 765

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 524

atggccacag caggaaatcc ctggggctgg ttctctgggt acctcatcct tgggtgtcgca 60  
 ggatcgctcg tctctggtag ctgcagccaa atcataaacg gcgaggactg cagcccgcac 120  
 tcgcagccct ggcaggcggc actggtcatg gaaaacgaat tggtctgctc gggcgctcctg 180  
 gtgcacccgc agtgggtgct gtcagccgca cactgtttcc agaactccta caccatcggtg 240  
 ctgggcctgc acagtcttga ggccgaccaa gagccaggga gccagatggt ggaggccagc 300  
 ctctccgtac ggcacccaga gtacaacaga cccttgctcg ctaacgacct catgctcatc 360  
 aagttggacg aatccgtgtc cgagtctgac accatccgga gcatcagcat tgcttcgcag 420  
 tgccctaccg cggggaaactc ttgcctcgtt tctggctggg gtctgctggc gaacggcaga 480  
 atgcctaccg tgctgcagtg cgtgaacgtg tcggtggtgt ctgaggaggt ctgcagtaag 540  
 ctctatgacc cgctgtacca cccagcatg ttctgcgccg gcggagggca agaccagaag 600  
 gactcctgca acggtgactc tggggggccc ctgatctgca acgggtactt gcagggcctt 660  
 gtgtctttcg gaaaagcccc gtgtggccaa gttggcgtgc caggtgtcta caccaacctc 720  
 tgcaaattca ctgagtggat agagaaaacc gtccaggcca gtttaa 765

&lt;210&gt; 525

&lt;211&gt; 254

&lt;212&gt; PRT

&lt;213&gt; Homo sapien



&lt;400&gt; 525

Met Ala Thr Ala Gly Asn Pro Trp Gly Trp Phe Leu Gly Tyr Leu Ile  
 1 5 10 15  
 Leu Gly Val Ala Gly Ser Leu Val Ser Gly Ser Cys Ser Gln Ile Ile  
 20 25 30  
 Asn Gly Glu Asn Cys Ser Pro His Ser Gln Pro Trp Gln Ala Ala Leu  
 35 40 45  
 Val Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln  
 50 55 60  
 Trp Val Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly  
 65 70 75 80  
 Leu Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met  
 85 90 95  
 Val Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu  
 100 105 110  
 Leu Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu  
 115 120 125  
 Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala  
 130 135 140  
 Gly Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg  
 145 150 155 160  
 Met Pro Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu Glu  
 165 170 175  
 Val Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys  
 180 185 190  
 Ala Gly Gly Gly Gln Asp Gln Lys Asp Ser Cys Asn Gly Asp Ser Gly  
 195 200 205  
 Gly Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly  
 210 215 220  
 Lys Ala Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn Leu  
 225 230 235 240  
 Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser  
 245 250

&lt;210&gt; 526

&lt;211&gt; 963

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 526

atgagttcct gcaacttcac acatgccacc tttgtgctta ttggtatccc aggattagag 60  
 aaagcccatt tctgggttgg cttcccctc ctttccatgt atgtagtggc aatgtttgga 120  
 aactgcatcg tggctcttcat cgtaaggacg gaacgcagcc tgcacgctcc gatgtacctc 180  
 tttctctgca tgcttgacgc cattgacctg gccttatcca catccaccat gcctaagatc 240  
 cttgcccttt tctggtttga ttcccagagag attagctttg aggcctgtct taccagatg 300  
 ttctttattc atgccctctc agccattgaa tccaccatcc tgctggccat ggcctttgac 360  
 cgttatgtgg ccattcgcca cccactgcgc catgctgcag tgctcaacaa tacagtaaca 420  
 gccagattg gcatcgctggc tgtggtccgc ggatccctct tttttttccc actgcctctg 480  
 ctgatcaagc ggctggcctt ctgcccactcc aatgtcctct cgcactccta ttgtgtccac 540  
 caggatgtaa tgaagtggc ctatgcagac actttgccca atgtggtata tggctttact 600  
 gccattctgc tggctcatggg cgtggacgta atgttcatct ccttgtccta ttttctgata 660  
 atacgaacgg ttctgcaact gccttccaag tcagagcggg ccaaggcctt tggaacctgt 720  
 gtgtcacaca ttggtgtggg actgccttc tatgtgccac ttattggcct ctacgttcta 780  
 caccgctttg gaaacagcct tcattccatt gtgcgtgttg tcattgggtga catctacctg 840  
 ctgctgcctc ctgtcatcaa tccatcatc tatggtgcc aaaccaaaaca gatcagaaca 900  
 cgggtgctgg ctatgttcaa gatcagctgt gacaaggact tgcaggctgt gggaggcaag 960  
 tga 963

Met	Ser	Ser	Cys	Asn	Phe	Thr	His	Ala	Thr	Phe	Val	Leu	Ile	Gly	Ile
				5					10					15	
Pro	Gly	Leu	Glu	Lys	Ala	His	Phe	Trp	Val	Gly	Phe	Pro	Leu	Leu	Ser
			20					25					30		
Met	Tyr	Val	Val	Ala	Met	Phe	Gly	Asn	Cys	Ile	Val	Val	Phe	Ile	Val
		35					40					45			
Arg	Thr	Glu	Arg	Ser	Leu	His	Ala	Pro	Met	Tyr	Leu	Phe	Leu	Cys	Met
	50					55					60				
Leu	Ala	Ala	Ile	Asp	Leu	Ala	Leu	Ser	Thr	Ser	Thr	Met	Pro	Lys	Ile
65					70					75					80
Leu	Ala	Leu	Phe	Trp	Phe	Asp	Ser	Arg	Glu	Ile	Ser	Phe	Glu	Ala	Cys
				85					90					95	
Leu	Thr	Gln	Met	Phe	Phe	Ile	His	Ala	Leu	Ser	Ala	Ile	Glu	Ser	Thr
			100					105					110		
Ile	Leu	Leu	Ala	Met	Ala	Phe	Asp	Arg	Tyr	Val	Ala	Ile	Cys	His	Pro
		115					120					125			
Leu	Arg	His	Ala	Ala	Val	Leu	Asn	Asn	Thr	Val	Thr	Ala	Gln	Ile	Gly
	130					135					140				
Ile	Val	Ala	Val	Val	Arg	Gly	Ser	Leu	Phe	Phe	Phe	Pro	Leu	Pro	Leu
145					150					155					160
Leu	Ile	Lys	Arg	Leu	Ala	Phe	Cys	His	Ser	Asn	Val	Leu	Ser	His	Ser
				165					170					175	
Tyr	Cys	Val	His	Gln	Asp	Val	Met	Lys	Leu	Ala	Tyr	Ala	Asp	Thr	Leu
			180					185					190		
Pro	Asn	Val	Val	Tyr	Gly	Leu	Thr	Ala	Ile	Leu	Leu	Val	Met	Gly	Val
		195					200					205			
Asp	Val	Met	Phe	Ile	Ser	Leu	Ser	Tyr	Phe	Leu	Ile	Ile	Arg	Thr	Val
	210					215					220				
Leu	Gln	Leu	Pro	Ser	Lys	Ser	Glu	Arg	Ala	Lys	Ala	Phe	Gly	Thr	Cys
225					230					235					240
Val	Ser	His	Ile	Gly	Val	Val	Leu	Ala	Phe	Tyr	Val	Pro	Leu	Ile	Gly
				245					250					255	
Leu	Ser	Val	Val	His	Arg	Phe	Gly	Asn	Ser	Leu	His	Pro	Ile	Val	Arg
			260					265					270		

Val Val Met Gly Asp Ile Tyr Leu Leu Leu Pro Pro Val Ile Asn Pro  
275 280 285

Ile Ile Tyr Gly Ala Lys Thr Lys Gln Ile Arg Thr Arg Val Leu Ala  
290 295 300

Met Phe Lys Ile Ser Cys Asp Lys Asp Leu Gln Ala Val Gly Gly Lys  
305 310 315 320

<210> 528  
<211> 20  
<212> DNA  
<213> Homo Sapien

<400> 528  
actatggtcc agaggctgtg 20

<210> 529  
<211> 20  
<212> DNA  
<213> Homo Sapien

<400> 529  
atcacctatg tgccgcctct 20

<210> 530  
<211> 1852  
<212> DNA  
<213> Homo sapiens

<400> 530  
ggcacgagaa ttaaaaccct cagcaaaaca ggcatagaag ggacatacct taaagtaata 60  
aaaaccacct atgacaagcc cacagccaac ataatactaa atgggggaaaa gttagaagca 120  
tttcctctga gaactgcaac aataaatata aggatgctgg attttgtcaa atgccttttc 180  
tgtgtctgtt gagatgctta tgtgactttg cttttaattc tgtttatgtg attatcacat 240  
ttattgactt gcctgtgtta gaccggaaga gctgggggtgt ttctcaggag ccaccgtgtg 300  
ctgcggcagc ttcgggataa cttgaggctg catcactggg gaagaaacac aytctgtcc 360  
gtggcgtgga tggctgagga cagagcttca gtgtggcttc tctgcgactg gcttcttcgg 420  
ggagtcttcc cttcatagtt catccatag gctccagagg aaaattatat tattttgtta 480  
tggtatgaaga gtattacgtt gtgcagatat actgcagtgt cttcatctct tgatgtgtga 540  
ttgggtaggt tccaccatgt tgccgcagat gacatgattt cagtacctgt gtctggctga 600  
aaagtgtttg tttgtgaatg gatattgtgg tttctggatc tcatcctctg tgggtggaca 660  
gctttctcca ccttgctgga agtgacctgc tgtccagaag tttgatggct gaggagtata 720  
ccatcgtgca tgcacttttc atttctgca tttcttctc cctggatgga cagggggagc 780  
ggcaagagca acgtgggcac ttctggagac cacaacgact cctctgtgaa gacgcttggtg 840  
agcaagaggt gcaagtgggt ctgccactgc ttcccctgct gcagggggag cggcaagagc 900  
aacgtgggtc cttggggaga ctacgatgac agcgccttca tggatcccag gtaccacgtc 960  
catggagaag atctggacaa gctccacaga gctgcctggt ggggtaaaagt cccagaaag 1020  
gatctcatcg tcatgctcag ggacacggat gtgaacaaga gggacaagca aaagaggact 1080  
gctctacatc tggcctctgc caatgggaat tcagaagtag taaaactcgt gctggacaga 1140  
cgatgtcaac ttaatgtcct tgacaacaaa aagaggacag ctctgacaaa ggccgtacaa 1200  
tgccaggaag ataatgtgc gttaatgttg ctggaacatg gcactgatcc aaatattcca 1260  
gatgagtatg gaaataccac tctacactat gctgtctaca atgaagataa attaatggcc 1320  
aaagcactgc tcttatacgg tgcgtatata gaatcaaaaa acaagcatgg cctcacacca 1380  
ctgctacttg gtatacatga gcaaaaacag caagtgggtga aatttttaat caagaaaaaa 1440  
gcgaatttaa atgcgctgga tagatatgga agaactgctc tcatacttgc tgtatgttgt 1500  
ggatcagcaa gtatagtcag cctctactt gagcaaaatg ttgatgtatc ttctcaagat 1560  
ctggaagagc ggccagagag tatgctgttt ctatgcatca tcatgtaatt tgccagttac 1620

tttctgacta caaagaaaaa cagatgttaa aaatctcttc tgaaaacagc aatccagaac 1680  
 aagacttaaa gctgacatca gaggaagagt cacaaaggct taaaggaagt gaaaacagcc 1740  
 agccagagct agaagattta tggctattga agaagaatga agaacacgga agtactcatg 1800  
 tgggattccc agaaaacctg actaacggtg ccgctgctgg caatggtgat ga 1852

<210> 531

<211> 879

<212> DNA

<213> Homo sapiens

<400> 531

atgcatcttt catttcctgc atttcttctt ccctggatgg acagggggag cggcaagagc 60  
 aacgtgggca cttctggaga ccacaacgac tcctctgtga agacgcttgg gagcaagagg 120  
 tgcaagtggg gctgccactg cttcccctgc tgcaggggga gcggcaagag caacgtgggc 180  
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Ile Gly His Lys Arg Arg Leu Glu Glu Asp Asp Met Tyr Ser Val Leu  
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 Asp Lys Glu Val Leu Arg Ala Glu Asn Asp Ala Gln Lys Pro Ser Leu  
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 Leu Gly Lys Ile Ile Asn Tyr Phe Glu Asn Tyr Asp Pro Met Asp Ser  
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 Thr Leu Ile Leu Ala Ile Leu His His Leu Tyr Phe Tyr His Val Gln  
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Arg Ile Gln Thr Phe Leu Leu Leu Asp Glu Ile Ser Gln Arg Asn Arg		
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Gln Leu Pro Ser Asp Gly Lys Lys Met Val His Val Gln Asp Phe Thr		
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Ala Phe Trp Asp Lys Ala Ser Glu Thr Pro Thr Leu Gln Gly Leu Ser		
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Phe Thr Val Arg Pro Gly Glu Leu Leu Ala Val Val Gly Pro Val Gly		
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Ala Gly Lys Ser Ser Leu Leu Ser Ala Val Leu Gly Glu Leu Ala Pro		
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Ser His Gly Leu Val Ser Val His Gly Arg Ile Ala Tyr Val Ser Gln		
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Gln Pro Trp Val Phe Ser Gly Thr Leu Arg Ser Asn Ile Leu Phe Gly		
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Gly Asp Arg Gly Thr Thr Leu Ser Gly Gly Gln Lys Ala Arg Val Asn		
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Gln Leu Gln Tyr Leu Lys Ala Ala Ser Gln Ile Leu Ile Leu Lys Asp		
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 Arg Thr Phe Ser Glu Ser Ser Val Trp Ser Gln Gln Ser Ser Arg Pro  
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Arg Lys Asn Leu Asp Pro Phe Asn Glu His Thr Asp Glu Glu Leu Trp 1090 1095 1100		
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Ser Val

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&lt;210&gt; 553

&lt;211&gt; 58

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 553

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Ser Ile Cys Asn Met Thr Cys Ala Ser Val Phe Phe Cys Asp Gln Lys
          5                      10                      15

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Phe Leu Thr Phe Ser Phe Leu Ser Met Val Glu Pro Pro Arg Ala Gly
          20                      25                      30

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Val Leu Asn Ser Gln Ala Thr Asp Ser Tyr Gln Ser Thr Asp Tyr Tyr
          35                      40                      45

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Glu Pro His His Thr Gly Gly Gly Glu His
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<210> 554  
 <211> 59  
 <212> PRT  
 <213> Homo sapiens

<400> 554  
 Leu Gln Lys Asn Lys Leu Arg Ala Ser Thr Asp Ser Thr Leu Trp Ile  
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 Cys Ala Ala Glu Ala Ser Thr Lys Pro Tyr Phe Tyr Thr Cys Leu Val  
                             20                            25                            30  
 Met Leu His Gly Gln Gly Leu Ala Leu Leu Ser Pro Thr Asn Leu Pro  
                             35                            40                            45  
 Glu Ile Leu Arg Phe Leu Phe Asn Gly Phe Leu  
                             50                            55

<210> 555  
 <211> 71  
 <212> PRT  
 <213> Homo sapiens

<400> 555  
 Leu Gly Arg Phe Ser Leu Ser Cys Lys Ser Gly His Ser Arg Gly Gln  
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 Pro Gln Leu Gly Ala Thr Ala Gln Gly Lys Val His Met Gly Leu Ser  
                             20                            25                            30  
 Thr Ala Gln Gly Ser Ile Gln Asp Ile Lys Val Pro His Ser Ile Asp  
                             35                            40                            45  
 Leu Val Ala Lys Lys Lys Lys Gln Thr Leu Ile Ser Phe Cys His Pro  
                             50                            55                            60  
 Ser Asp Pro Leu Glu Leu Leu  
                             65                            70

<210> 556  
 <211> 81  
 <212> PRT  
 <213> Homo sapiens

<400> 556  
 Asn His Pro Glu Gln Gly Ser Ser Thr Pro Arg Pro Gln Thr His Thr  
                             5                            10                            15  
 Ser Pro Arg Thr Ile Met Asn His Thr Thr Gln Glu Glu Val Ser Thr  
                             20                            25                            30  
 Arg Gln Ala Lys Glu Ala Ser Pro Val Leu Thr Ala Thr Arg His Gly  
                             35                            40                            45  
 Ser Tyr Tyr Ser Leu Asn Ser Ala Ser Thr Gln Ile Ser Asp Asn Ile

203

50                      55                      60  
 Arg Asn Ser Leu Glu His Glu Pro Cys Cys Glu Leu Pro Ile Arg Arg  
 65                      70                      75                      80

Ile

<210> 557  
 <211> 54  
 <212> PRT  
 <213> Homo sapiens

<400> 557  
 Ser Leu Ser Ala Thr Pro Leu Thr Leu Trp Asn Ser Ser Asp Pro Leu  
                                  5                      10                      15

Glu Gln Ala Tyr Leu Ile Ser Ala Arg Glu Lys Thr Asn Asn Gly Leu  
                                  20                      25                      30

Lys Gly Ser Leu Thr Met Lys Val Ser Ala Asn Ser Trp Leu Arg Cys  
                                  35                      40                      45

Gly Phe His Ile Arg Phe  
                                  50

<210> 558  
 <211> 77  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> VARIANT  
 <222> (1)...(77)  
 <223> Xaa = Any amino acid

<400> 558  
 Asn Asp Arg Asp Arg Asn Ser Asn Lys Val Ile Xaa Lys Ala Asn Leu  
                                  5                      10                      15

Ile Tyr Phe Thr Asn Leu Thr Ser Cys Leu Ser Val Gln Asn Gln Thr  
                                  20                      25                      30

Phe Thr Cys Thr Lys Arg His Lys His Leu Gln Cys Ser Ser Val His  
                                  35                      40                      45

Leu Cys Lys Ile Pro Pro Arg Leu Lys Gly Arg Asp Lys Lys Lys Lys  
                                  50                      55                      60

Pro Ser Tyr Leu Ser Gly Val Leu His Ser Arg Ser Tyr  
                                  65                      70                      75

<210> 559  
 <211> 50  
 <212> PRT



<213> Homo sapiens

<400> 559

Thr Leu Pro Pro Leu Arg Ser Val Ile Thr Leu Glu Thr His Trp Ser  
5 10 15

Thr Asn Pro Val Val Asn Cys Leu Ser Glu Gly Ser Arg Leu Cys Ala  
20 25 30

Ser Tyr Glu Asn Leu Met Pro Asp Asp Leu Ser Leu Ser His Phe Ala  
35 40 45

Pro Arg  
50

<210> 560

<211> 56

<212> PRT

<213> Homo sapiens

<400> 560

Ile Gly Ser Leu Lys Gly Pro Thr Thr Ala Gly Ser His Cys Ser Gly  
5 10 15

Glu Gly Ser Tyr Gly Thr Phe Tyr Cys Pro Arg Phe Tyr Thr Gly Tyr  
20 25 30

Lys Gly Ala Ser Gln Tyr Arg Ser Gly Ser Lys Glu Glu Glu Thr Asn  
35 40 45

Thr Asp Leu Phe Leu Pro Pro Leu  
50 55

<210> 561

<211> 57

<212> PRT

<213> Homo sapiens

<220>

<221> VARIANT

<222> (1)...(57)

<223> Xaa = Any amino acid

<400> 561

Val Leu His Leu Asp Gln Met Asn Asn Val Gly Ile Xaa Met Asp Lys  
5 10 15

Gly Leu Lys Ser Pro Glu Ile Lys Asn Pro Ala Pro Thr Gly Thr Ser  
20 25 30

Asn Leu Ser Cys Phe Leu Ser Xaa Phe Trp Leu Met Gln Gly Thr Asn  
35 40 45

Ser Leu Pro Arg Glu Asn Tyr Leu Asn  
50 55

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<220>  
<221> VARIANT  
<222> (1)...(59)  
<223> Xaa = Any amino acid.
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<400> 562
Asp Leu Tyr Pro Xaa Arg Ser Gln His Cys Ser Phe Asp Pro Ser Val
      5                      10                      15
Ala Pro Met His Gly Ile Lys Asn Ser Ile Thr Ser Leu Ile Phe Leu
      20                      25                      30
Ile Ser Tyr Leu Xaa Leu Glu Met Ser Ser Leu Ser Glu Ser Leu Val
      35                      40                      45
Leu Ser Ser Gly Asp Tyr Val Leu Asp Thr Pro
      50                      55

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<210> 563
<211> 79
<212> PRT
<213> Homo sapiens
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<400> 563
Cys Phe Leu Phe Pro Tyr Leu Trp Leu Tyr Ala Gln Pro Leu Phe Pro
      5                                10                        15

Lys Gln Gln Pro Pro Ala Leu Ala Pro Gly His Pro Asp Phe Ile His
      20                                25                        30

Thr Gln Asn Glu Gln Ile Asp Pro Ser Pro His Ile Gln Asn Leu Met
      35                                40                        45

Trp Asn Pro His Leu Ser Gln Glu Leu Ala Glu Thr Phe Met Val Arg
      50                                55                        60

Asp Pro Leu Arg Pro Leu Leu Val Phe Ser Leu Ala Asp Ile Arg
      65                                70                        75
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<210> 564
<211> 64
<212> PRT
<213> Homo sapiens
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<400> 564  
Ala Cys Ser Lys Gly Ser Glu Glu Phe Gln Arg Val Arg Gly Val Ala  
5 10 15  
Glu Arg Asp Gln Cys Leu Phe Leu Leu Leu Cys Tyr Gln Ile Tyr Thr  
20 25 30

Val Arg His Leu Tyr Ile Leu Tyr Arg Thr Leu Gly Ser Arg Lys Ser  
           35                          40                          45

His Met Asn Leu Pro Leu Ser Ser Gly Ser Gln Leu Trp Leu Ala Pro  
           50                          55                          60

<210> 565

<211> 57

<212> PRT

<213> Homo sapiens

<220>

<221> VARIANT

<222> (1)...(57)

<223> Xaa = Any amino acid

<400> 565

Leu Tyr Tyr Cys Ser Tyr Leu Cys His Phe Arg Thr Ala Leu Ile Leu  
                           5                          10                          15

Ala Val Cys Cys Gly Ser Ala Ser Ile Val Ser Leu Leu Leu Glu Gln  
                           20                          25                          30

Asn Ile Asp Val Ser Ser Gln Asp Leu Ser Gly Gln Thr Ala Arg Glu  
           35                          40                          45

Tyr Ala Val Ser Ser Xaa His Asn Val  
           50                          55

<210> 566

<211> 55

<212> PRT

<213> Homo sapiens

<400> 566

Ile Leu Leu Glu Phe Phe Arg Asn Gln Arg Gly Ser Leu Asn Pro Arg  
                           5                          10                          15

Lys Thr Val Pro Phe Ile Lys Ser Glu Gly Gly Glu Lys Lys Gly His  
                           20                          25                          30

Cys Asn His Ser Val Val Ser Ile Asp Ser Ala Ala Ala Leu Leu Pro  
           35                          40                          45

Leu Lys Leu Val Leu Leu Pro  
           50                          55

<210> 567

<211> 51

<212> PRT

<213> Homo sapiens

<400> 567

Tyr Ser Asp Phe Asp Val Phe Cys Ser His Thr Tyr Gly Tyr Met Leu

5 10 15  
 Ser His Cys Ser Gln Ser Ser Ser Pro Leu Leu Trp Pro Leu Gly Ile  
 20 25 30  
 Leu Thr Leu Ser Thr His Lys Met Ser Lys Leu Thr Leu Pro Pro Ile  
 35 40 45  
 Phe Arg Thr  
 50

<210> 568  
 <211> 75  
 <212> PRT  
 <213> Homo sapiens

<400> 568  
 Lys Val Gly Glu Tyr Ile Leu Gln Ser Leu Leu Arg Ile Arg Lys Ile  
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 Tyr Val Ala Phe Asn Ser Val Pro Ser Thr Cys Leu Leu Ala Ser Leu  
 20 25 30  
 Thr Glu Thr Pro Val Thr Thr Ile Leu Thr Ile Ile Ile Asn Leu Thr  
 35 40 45  
 Cys Phe Gln His Ala Glu Ser Ser Tyr Leu Phe Tyr Pro Leu Ala Asp  
 50 55 60  
 Phe Leu Leu Gln His Ile Ser Leu Gly Lys Leu  
 65 70 75

<210> 569  
 <211> 4809  
 <212> DNA  
 <213> Homo sapiens

<400> 569  
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 aatggacttg cttcaaagtg gaggcaggca gatccttcag acgggtatat ggagccctgt 240  
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&lt;210&gt; 570

&lt;211&gt; 951

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 570

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&lt;210&gt; 571

&lt;211&gt; 819

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 571

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&lt;210&gt; 572

&lt;211&gt; 203

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 572

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 attgtgttgg gcccaacaca atggagccac cacatccagc ctgccacata cttttaaaact 180  
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<210> 573

<211> 132

<212> PRT

<213> Homo sapiens

<400> 573

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 Arg Glu Arg Val Arg Gly Glu Thr Ala Thr Asn Phe Phe Phe Leu Arg  
                                   20                                  25                                  30  
 Gln Glu Ser Gly Pro Val Ala Gln Ala Gly Val Gln Trp His Asp Leu  
                                   35                                  40                                  45  
 Ser Ser Leu Gln Pro Leu Pro His Arg Phe Lys Gln Phe Ser Cys Leu  
                                   50                                  55                                  60  
 Ser Leu Pro His Ser Trp Asp His Arg Tyr Ala Pro Pro His Leu Ala  
                                   65                                  70                                  75                                  80  
 Asn Phe Cys Ser Phe Ser Arg Asp Gly Val Ser Leu Cys Cys Ser Gly  
                                   85                                  90                                  95  
 Trp Ser Lys Thr Pro Gly Leu Gln Gln Ser Ala Cys Leu Gly Leu Pro  
                                   100                                  105                                  110  
 Lys Cys Trp Gly Tyr Arg His Lys Pro Pro His Pro Ala Cys His Ile  
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 Leu Leu Asn Tyr  
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<210> 574

<211> 62

<212> PRT

<213> Homo sapiens

<400> 574

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                                   20                                  25                                  30  
 Glu Arg Thr Ser Glu Gly Gly Asp Cys His Lys Leu Phe Phe Phe Glu  
                                   35                                  40                                  45  
 Thr Arg Val Trp Pro Cys Cys Pro Gly Trp Ser Ala Val Ala  
                                   50                                  55                                  60

<210> 575

<211> 76  
 <212> PRT  
 <213> Homo sapiens

<400> 575  
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                                   20                                  25                                  30  
 Ser Leu Glu Pro Gly Arg Leu Arg Glu Glu Asn Arg Leu Asn Pro Gly  
                                   35                                  40                                  45  
 Gly Arg Gly Cys Ser Glu Pro Arg Ser Cys Cys Cys Thr Pro Ala Trp  
                                   50                                  55                                  60  
 Ser Thr Glu Gln Asp Ser Ala Ser Lys Thr Asn Lys  
                                   65                                  70                                  75

<210> 576  
 <211> 68  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> VARIANT  
 <222> (1)...(68)  
 <223> Xaa = Any Amino Acid

<400> 576  
 Met Leu Gly Lys Ser Arg Ala Val Cys Leu Pro Ser Thr Thr Val Thr  
                                   5                                  10                                  15  
 Thr Val Cys Tyr Leu Ala Ser Ser Ser Ala Ser Arg Glu Thr Ala Thr  
                                   20                                  25                                  30  
 Arg Gln Ala Pro Gly Asn Trp Lys Met Xaa Ser Lys Cys His Ala Gln  
                                   35                                  40                                  45  
 Leu Leu Phe Thr Phe Tyr Leu Asn His Phe Tyr Gln Ile Arg Leu Asn  
                                   50                                  55                                  60  
 Pro Gly Tyr Ser  
 65

<210> 577  
 <211> 57  
 <212> PRT  
 <213> Homo sapiens

<400> 577  
 Met Tyr Leu Glu Asn Ser Phe Tyr Cys Gln Met Ile Leu Leu Lys Arg  
                                   5                                  10                                  15  
 Cys Arg Leu Ser Lys Ile Ser Thr Gln Arg Val Val Pro Asp Gly Pro



20 25 30

Pro Ala Pro Val Pro Gly Ser Phe Pro Met Phe Pro Arg Phe Gly Phe  
 35 40 45

Arg Leu Ala Pro Pro Ala Asp Thr Pro  
 50 55

<210> 578  
 <211> 51  
 <212> PRT  
 <213> Homo sapiens

<400> 578  
 Met Gln Leu Ile Tyr Leu Cys Phe Leu Gly Leu Leu Tyr Ile Arg His  
 5 10 15

His Asp Ser Gln Ser Phe Val Ile Leu Tyr Tyr Lys Lys Leu Asn Tyr  
 20 25 30

Tyr Phe Lys Tyr Gly Gln Ile Arg Ala Phe His Ile Ala Lys Val Tyr  
 35 40 45

Gln Pro His  
 50

<210> 579  
 <211> 56  
 <212> PRT  
 <213> Homo sapiens

<400> 579  
 Met His Phe Thr Phe Met Gln Leu Ile Tyr Leu Cys Phe Leu Gly Leu  
 5 10 15

Leu Tyr Ile Arg His His Asp Ser Gln Ser Phe Val Ile Leu Tyr Tyr  
 20 25 30

Lys Lys Leu Asn Tyr Tyr Phe Lys Tyr Gly Gln Ile Arg Ala Phe His  
 35 40 45

Ile Ala Lys Val Tyr Gln Pro His  
 50 55

<210> 580  
 <211> 67  
 <212> PRT  
 <213> Homo sapiens

<400> 580  
 Met Glu Leu Arg Thr Lys Ala Leu Arg Thr Ala Gln Gln Leu Thr Ser  
 5 10 15

Cys Val Thr Ala Leu Lys Ala Ala Gly Pro Pro Leu Thr Phe Trp Lys  
 20 25 30

Gly Lys Trp Val Gln Cys Cys Leu Pro Leu Trp Gly Leu Leu Gly Ser  
                   35                                  40                                  45

His Ala Phe Tyr Ile Tyr Ala Val Asp Ile Phe Met Phe Pro Gly Ser  
           50                                  55                                  60

Phe Ile His  
   65

<210> 581

<211> 77

<212> PRT

<213> Homo sapiens

<400> 581

Met Leu Glu Val Lys Phe Glu Val Ser Leu Arg Pro Thr Gly Asn Glu  
                                   5                                  10                                  15

Thr Ala Gly Gln Thr His Gly Thr Gln Asp Lys Gly Ser Lys Asp Ser  
                   20                                  25                                  30

Thr Ala Ala Asp Ile Leu Cys Asp Ser Leu Glu Ser Ser Arg Pro Ala  
                   35                                  40                                  45

Ala His Ile Leu Glu Gly Lys Met Gly Thr Met Leu Ser Ala Thr Leu  
           50                                  55                                  60

Gly Pro Ser Trp Val Thr Cys Ile Leu His Leu Cys Ser  
   65                                  70                                  75

<210> 582

<211> 51

<212> PRT

<213> Homo sapiens

<400> 582

Met Leu Phe Leu Gln Thr Ile Asp Thr Lys Cys Thr Gly Ile Glu Ile  
                                   5                                  10                                  15

Asn Arg Asn Trp Ser Lys Val Trp His Thr His Ser His Val Asp Val  
                   20                                  25                                  30

Lys Leu Cys Leu Glu Phe Leu Cys Gly Val Trp Phe Gly Leu Gly Phe  
                   35                                  40                                  45

Leu Gly Val  
   50

<210> 583

<211> 60

<212> PRT

<213> Homo sapiens

<400> 583

214

Met Ser Thr Ser Asp Gly Phe Ala Pro Pro Pro Gln Leu Gly Ser Arg  
                                   5                                  10                                  15

Cys Ser His Ile Arg Gly Pro Ile Lys Ile Ala Arg Asn Lys Phe Pro  
                                   20                                  25                                  30

Arg Thr Leu Thr Ser Gln Glu Leu Arg Arg Phe Ala Glu Tyr Ser Gly  
                                   35                                  40                                  45

Met Met Phe Gly Asp Gln Thr Thr Ala Gly Gln Lys  
                                   50                                  55                                  60

&lt;210&gt; 584

&lt;211&gt; 76

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 584

Met Cys Leu Cys Ile Pro Leu Gly Gly Tyr Gln Glu Leu Cys His Cys  
                                   5                                  10                                  15

Met Ser Thr Ser Asp Gly Phe Ala Pro Pro Pro Gln Leu Gly Ser Arg  
                                   20                                  25                                  30

Cys Ser His Ile Arg Gly Pro Ile Lys Ile Ala Arg Asn Lys Phe Pro  
                                   35                                  40                                  45

Arg Thr Leu Thr Ser Gln Glu Leu Arg Arg Phe Ala Glu Tyr Ser Gly  
                                   50                                  55                                  60

Met Met Phe Gly Asp Gln Thr Thr Ala Gly Gln Lys  
                                   65                                  70                                  75

&lt;210&gt; 585

&lt;211&gt; 50

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 585

Met Val Tyr Arg Phe Gly Gln Met Ser Asp Asn Pro Phe Tyr Ile Leu  
                                   5                                  10                                  15

Ala Ser Leu Gly Ser Ser Ser Cys Arg Asn Gly Leu Ala Ser Lys Trp  
                                   20                                  25                                  30

Arg Gln Ala Asp Pro Ser Asp Gly Tyr Met Glu Pro Cys Phe Gln Leu  
                                   35                                  40                                  45

Leu Phe  
                                   50

&lt;210&gt; 586

&lt;211&gt; 60

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

Leu Gln Phe Arg Gln Tyr Asn Lys Ser Val His Glu Val Asn Leu Lys  
20 25 30

Gly Ala Cys Phe Thr Val Ala Gly Leu Pro Arg Ala Trp Thr Thr Gln  
           35                  40                  45  
 Tyr Ser Ile Ile Asp Lys Arg Ile Arg Gln Glu Ile Tyr Thr Cys Cys  
           50                  55                  60  
 Leu Ala Phe Val Val Ile Tyr Thr Asn Glu Asn Met Tyr Tyr Ser Tyr  
       65                  70                  75                  80  
 Ile

<210> 589  
 <211> 157  
 <212> PRT  
 <213> Homo sapiens

<400> 589  
 Met Thr Met Cys Leu Cys Val Ala Pro Met Gly Arg Ala Thr Arg Met  
                   5                  10                  15  
 Ser Val Thr Cys Asp Arg Leu His Ala Asn Ser Arg Val Arg Tyr Leu  
                   20                  25                  30  
 Trp Cys Gln Lys Asp His Val Pro Gln Met Gln Asp Gln Asp Leu Glu  
           35                  40                  45  
 Met Glu Ser Met Lys Ala Leu Glu Lys Leu Val Lys Arg Arg His Pro  
       50                  55                  60  
 Pro Val Ile Phe Ala Ser Leu Val Gln Asn Val Thr Lys Met Pro Arg  
       65                  70                  75                  80  
 Met Ser Gly Val Cys Val Ile Leu Thr Val Leu Lys Pro Thr Ser Ile  
                   85                  90                  95  
 Pro Ser Ala Leu Leu Met Gly Asn Leu Met Ile Met His Ala Lys Ser  
           100                  105                  110  
 Lys Lys His Arg Val Arg Asn Arg Arg Lys Leu Lys Ser Cys Leu Trp  
           115                  120                  125  
 Val Asp Val Lys Ile Thr Gln Leu Gln Leu Leu Ser Leu Lys Met Gly  
       130                  135                  140  
 Ile Met Gln Glu Gln Ile Met Gln Arg Met Leu Thr Asn  
       145                  150                  155

<210> 590  
 <211> 347  
 <212> PRT  
 <213> Homo sapiens

<400> 590  
 Met Leu Leu Ile Val Ala Arg Pro Val Lys Leu Ala Ala Phe Pro Thr  
                   5                  10                  15

Ser Leu Ser Asp Cys Gln Thr Pro Thr Gly Trp Asn Cys Ser Gly Tyr  
 20 25 30  
 Asp Asp Arg Glu Asn Asp Leu Phe Leu Cys Asp Thr Asn Thr Cys Lys  
 35 40 45  
 Phe Asp Gly Glu Cys Leu Arg Ile Gly Asp Thr Val Thr Cys Val Cys  
 50 55 60  
 Gln Phe Lys Cys Asn Asn Asp Tyr Val Pro Val Cys Gly Ser Asn Gly  
 65 70 75 80  
 Glu Ser Tyr Gln Asn Glu Cys Tyr Leu Arg Gln Ala Ala Cys Lys Gln  
 85 90 95  
 Gln Ser Glu Ile Leu Val Val Ser Glu Gly Ser Cys Ala Thr Asp Ala  
 100 105 110  
 Gly Ser Gly Ser Gly Asp Gly Val His Glu Gly Ser Gly Glu Thr Ser  
 115 120 125  
 Gln Lys Glu Thr Ser Thr Cys Asp Ile Cys Gln Phe Gly Ala Glu Cys  
 130 135 140  
 Asp Glu Asp Ala Glu Asp Val Trp Cys Val Cys Asn Ile Asp Cys Ser  
 145 150 155 160  
 Gln Thr Asn Phe Asn Pro Leu Cys Ala Ser Asp Gly Lys Ser Tyr Asp  
 165 170 175  
 Asn Ala Cys Gln Ile Lys Glu Ala Ser Cys Gln Lys Gln Glu Lys Ile  
 180 185 190  
 Glu Val Met Ser Leu Gly Arg Cys Gln Asp Asn Thr Thr Thr Thr Thr  
 195 200 205  
 Lys Ser Glu Asp Gly His Tyr Ala Arg Thr Asp Tyr Ala Glu Asn Ala  
 210 215 220  
 Asn Lys Leu Glu Glu Ser Ala Arg Glu His His Ile Pro Cys Pro Glu  
 225 230 235 240  
 His Tyr Asn Gly Phe Cys Met His Gly Lys Cys Glu His Ser Ile Asn  
 245 250 255  
 Met Gln Glu Pro Ser Cys Arg Cys Asp Ala Gly Tyr Thr Gly Gln His  
 260 265 270  
 Cys Glu Lys Lys Asp Tyr Ser Val Leu Tyr Val Val Pro Gly Pro Val  
 275 280 285  
 Arg Phe Gln Tyr Val Leu Ile Ala Ala Val Ile Gly Thr Ile Gln Ile  
 290 295 300  
 Ala Val Ile Cys Val Val Val Leu Cys Ile Thr Arg Lys Cys Pro Arg  
 305 310 315 320

Ser Asn Arg Ile His Arg Gln Lys Gln Asn Thr Gly His Tyr Ser Ser  
 325 330 335

Asp Asn Thr Thr Arg Ala Ser Thr Arg Leu Ile  
 340 345

<210> 591  
 <211> 565  
 <212> DNA  
 <213> Homo sapien

<400> 591  
 actaaagcaa atgaacaagc tgacttgcta gtatcatctg cattcattga agcacaagaa 60  
 cttcatgcct tgactcatgt aaatgcaata ggattaaaaa ataaatttga tatcacatgg 120  
 aaacagacaa aaaatattgt acaacattgc acccagtgtc agattctaca cctggccact 180  
 caggaagcaa gagttaatcc cagaggtcta tgtcctaata tgttatggca aatggatgtc 240  
 atgcacgtac cttcatttgg aaaattgtca tttgtccatg tgacagttga tacttattca 300  
 catttcatat gggcaacctg ccagacagga gaaagtactt cccatgttaa aagacattta 360  
 ttatcttggtt ttctgtgcat gggagttcca gaaaaagtta aaacagacaa tgggccaggt 420  
 tactgtagta aagcatttca aaaattctta aatcagtggg aaattacaca tacaatagga 480  
 attctctata attccaagg acaggccata attgaaggaa ctaatagaac actcaaagct 540  
 caattgggta aacaaaaaaa aaaaa 565

<210> 592  
 <211> 188  
 <212> PRT  
 <213> Homo sapien

<400> 592  
 Thr Lys Ala Asn Glu Gln Ala Asp Leu Leu Val Ser Ser Ala Phe Ile  
 1 5 10 15  
 Glu Ala Gln Glu Leu His Ala Leu Thr His Val Asn Ala Ile Gly Leu  
 20 25 30  
 Lys Asn Lys Phe Asp Ile Thr Trp Lys Gln Thr Lys Asn Ile Val Gln  
 35 40 45  
 His Cys Thr Gln Cys Gln Ile Leu His Leu Ala Thr Gln Glu Ala Arg  
 50 55 60  
 Val Asn Pro Arg Gly Leu Cys Pro Asn Val Leu Trp Gln Met Asp Val  
 65 70 75 80  
 Met His Val Pro Ser Phe Gly Lys Leu Ser Phe Val His Val Thr Val  
 85 90 95  
 Asp Thr Tyr Ser His Phe Ile Trp Ala Thr Cys Gln Thr Gly Glu Ser  
 100 105 110  
 Thr Ser His Val Lys Arg His Leu Leu Ser Cys Phe Pro Val Met Gly  
 115 120 125  
 Val Pro Glu Lys Val Lys Thr Asp Asn Gly Pro Gly Tyr Cys Ser Lys  
 130 135 140  
 Ala Phe Gln Lys Phe Leu Asn Gln Trp Lys Ile Thr His Thr Ile Gly  
 145 150 155 160  
 Ile Leu Tyr Asn Ser Gln Gly Gln Ala Ile Ile Glu Gly Thr Asn Arg  
 165 170 175  
 Thr Leu Lys Ala Gln Leu Val Lys Gln Lys Lys Lys  
 180 185

<210> 593  
 <211> 271

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(271)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 593

actttatggt	cnagtgcana	aanccncctg	gattgccacc	ntactctcag	ggctgtgant	60
tgtgcnccca	nagcaacctg	ggcacgcggg	gacagggggg	ccnacaattg	agggagcggt	120
gtccctagct	ggggtctata	catgncnggg	naagggcngc	tgagtnccat	nagcaaagga	180
nctagnatnt	gcgggggtgc	ggcctgggcc	taccctttna	agcatccntn	gatccactcc	240
angaanccng	gggtagnacg	gtttncaca	a			271

&lt;210&gt; 594

&lt;211&gt; 376

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(376)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 594

cctttggggg	nggggggaac	ctttaccatt	gtcccccttt	atttcatttg	gttnggggtc	60
gcgccctcnn	gggccaacaa	agttatcgtn	nttgaagaga	anattttttt	ggnttngncc	120
cgattaagcg	ncaaatgtgt	agcaaaangc	cgtgccactt	gtggcgtagc	tncgtcgggt	180
cgattcgacg	acaaggcgtn	gcgcgntanc	gttagtctcn	aatngaccn	gtggcatgag	240
cccacgangg	nttcgtgtcg	tcacatggnc	tctagacata	acgcncncn	ttttttncag	300
agggggntgc	cgcccttagg	gagggnagggg	tggggacact	agccaancca	nantctnacc	360
ccattgaaga	aaaggn					376

&lt;210&gt; 595

&lt;211&gt; 242

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(242)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 595

agnctgctgn	tcgtnccctn	tatgtggctt	catnntgagg	acaanagtng	cactgaggct	60
tgnngnatgcc	aggcaaggnc	aagctggctc	aaaaagcatc	caccacctc	tgnaangggg	120
atgccangag	cangtgcacc	agtcccaact	angagnccn	ggcatgntac	atcttcttcc	180
accctnaaa	ntttngngcta	caangnccat	ttttcttttt	ctcttaaggg	ncnctnggct	240
tc						242

&lt;210&gt; 596

&lt;211&gt; 535

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature



&lt;222&gt; (1)...(535)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 596

accagttgga	tactgctaaa	nagatatatta	tgcagcctca	tatgttaagt	cgtatatattt	60
gaaagctttt	taaatttttt	ctttaagaag	atttttagatg	cttatcactg	agtaccagag	120
ggatgttaggc	tgatgccctt	atcaacaaaag	tcagggactg	tggcacacaa	ggattgacta	180
ctgcagacac	ggccacaatg	ctacctctag	agggcctgaa	tccccctgcc	ctctctggtg	240
gggagaaggg	ctggcagagc	cattagcatg	ggctccggcc	aatcctggcc	actttgacac	300
tcctggtgct	gaccagggt	cctggaggaa	gggatgaggt	gggcagtaga	gatgctcagg	360
gcagtggccc	ctttccatcc	acactggaac	tatttcagta	ttttaccacc	aattcagcca	420
ttcccttggtg	cgctggctga	acatcagccc	tgtctcaggt	ctcagtttcc	cctttgtaaa	480
gggaaagctc	tggattcagg	gagtgatgaa	gaggtcatca	tggctcttgag	aattc	535

&lt;210&gt; 597

&lt;211&gt; 257

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(257)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 597

tttcnatacc	caaaantacc	ccatattang	accanacatt	tgtctnggaa	aaattaccat	60
tntntaant	ttgggccacc	tgagannaaa	tggtgtgaat	ncatgataag	atggancagn	120
attnctctta	agatnngatn	agaccccggt	tttcacggaa	catatccaag	nacccaatag	180
gnaacaagcc	acgggnggag	tcacaaacat	atattcttta	ctctcataat	ccgtnnncaca	240
naactnttgn	acttgac					257

&lt;210&gt; 598

&lt;211&gt; 222

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(222)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 598

nntgntacc	gtcnaaactt	nncttggtac	ccgagctcgg	atccactagt	ccagtgtggt	60
ggaattccat	tgtgttgggc	tataagctgt	aatagtggag	ncgtgctngg	ttcattgcan	120
nagnccctcc	gcannacacn	ttggnacaac	ctgtgagnag	gcnataaatt	attcacataa	180
tcatcactgc	atgaanctga	ctcaaacgca	tccacntaca	cc		222

&lt;210&gt; 599

&lt;211&gt; 238

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(238)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 599

gcatgacatc	ancgatgtnt	ttggnnacct	ganattngct	aaaactngng	natgccgggn	60
atgnagggtt	ggtantgatc	tatgcactca	catctcatgg	ggacgtttca	tgtggagtg	120
tcgacaangt	tgctgnancn	gagaagtgat	gatctcagtt	gaaaggggtca	tgtgaataca	180
cnttacactt	gaaaaagaag	cacattggga	atatcacgaa	acgnccacca	acatcctg	238

&lt;210&gt; 600

&lt;211&gt; 232

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(232)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 600

cgaactat	agactaccta	ggaaaattat	tttagtatca	gaagaatata	aggggtgtag	60
tactcatcag	agctaaatga	gagcgcttta	aaaatgttag	tttgtcttcc	gccatttcta	120
cagaaagctg	caatttcagg	ttttcaacct	aataggtgat	atttaanaaa	aaaaaaaagc	180
aatcgcaaat	agccccactg	cttttacaaa	tcattttttc	cccaacacaa	tg	232

&lt;210&gt; 601

&lt;211&gt; 547

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(547)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 601

cattgtgttg	gggaaaaaat	gatttgtata	agcagtgggg	ctatttgcca	ttgctttttt	60
tttttcttaa	atatcaccta	ttaggttgaa	aacctgaaat	tgcagctttc	tgtagaaatg	120
gcggaagaca	aactaacatt	tttaaagcgc	tctcatttag	ctctgatgag	tactacaccc	180
ctnatattct	tctgatacta	aaataatttt	cctagtgtag	tctaaacttt	tttaaaaaga	240
catgtaatcc	gcggagtttag	taactcaaaa	cgagtgcata	tnggaagtat	cgcagccggt	300
nctggatnaa	attcccagct	tgctngcttg	ctnagccggg	gggcggtnaa	aaaaacatct	360
gcagcccngg	ggnaaaaacc	ttcgcatgtg	tcttacgtgt	ttacgttatt	ttatttcctt	420
nnagcaaggc	nggganttgg	ggactcgaaa	tggtagagtt	gggctgggga	tcgcccttgt	480
tacataaaag	ncgtccagaa	gagggacggt	tacaggcnng	ganctccaaa	ggtcagtcct	540
tgccatt						547

&lt;210&gt; 602

&lt;211&gt; 826

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(826)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 602

cgggggggnt	tacgtctctc	tggacgcttt	tattgtacca	gggcgatccc	agcccaactg	60
taccattcga	gtccctactc	ctgccttgct	ctagggaaat	aaaataacgt	aaacacgtaa	120
gaacaatgcy	aaagcggttt	cttccctagc	ctgcagattg	tcttcttcac	cgccccgtct	180
tagctagcta	gctagctggg	aatttaatcc	agaaacggct	tgcgatacct	cctagatgca	240

ctcgttttga	gttacaaact	ccgcggatta	catgtctttt	taaaaaagtt	tagactacac	300
tagggaaaat	tatttttagta	tcagaagaat	atcaggggggt	gtagtactca	tcagagctna	360
atgagagcgc	tttaaaaatg	ttagtttgtc	ttccgccatt	tctacagaaa	gctgcaattt	420
caggttttca	ncctaataag	tgatatntaa	gaaaaaaaaa	acaatcgcan	atagcccact	480
gctttttaca	atcatttttc	tcttctaggt	atagcctgtc	aggtggccta	atgtattttt	540
gacatctcta	ggaattttta	tagaccagaa	atgggtgcc	gagatatgcc	tgactaatac	600
ttaagtgggg	atttatgtat	ttctcaanca	agtgtattaa	gcaaaactag	gcacgaatga	660
aatcaagatc	tttaggccag	aaatcatgaa	nanttttana	attattttan	gaatctgtgg	720
cttctcttct	taaaaatngaa	aaaaaaattg	tttaaacc	naaggtctga	atacccaagc	780
nccctgaacn	anagaacaan	gccggagcac	cccctcccaa	atcccc		826

&lt;210&gt; 603

&lt;211&gt; 817

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(817)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 603

nnangacttt	tgtggtntta	tacaattntt	ttttctattt	ctatgaagag	aaagccacag	60
agtcctaaaa	taattctaaa	actcatcatg	actttcttgc	ctaaaagatc	ttgatttcaa	120
tcgtgcctag	ttttgcttta	atcacttgct	tgagaaatac	ataaatcccc	acttaagatt	180
agtgacggca	tatctctggc	acccatttct	ggttctatta	aaattcctag	agatgtcaaa	240
aattacatta	ggccacctga	caggctatac	ctagaagaga	aaaaatgatt	tgtaaaagca	300
gtggggctat	ttgcgattgc	tttttttttt	tcttaaatat	cacctattag	gttgaaaacc	360
tgaaattgca	gctttctgta	gaaatggcgg	aagacaaact	aacattttta	aagcgctctc	420
atttagctct	gtgagtagt	acacccctga	tattcttctg	atactaaaat	aattttccta	480
gtgtagtcta	aactttttta	aaaagacatg	taatccgagg	agtttgtaac	tcaaaacgag	540
tgcatctagg	aggtatcgca	agccgtttct	ggattaaatt	cccagctagc	ttgcttgctt	600
agcaggggag	ggnaaanaag	acatctgcag	cctagggaag	aaaacctttc	gcattgttct	660
tacgtgttta	cggtatttta	tttctctana	caaggcngaa	ttgggactcg	aatggttcag	720
ttgggggtgg	ggatcccctg	gtncataaaa	ngtcanaaag	anggtacagg	cggaacncca	780
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&lt;211&gt; 694

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(694)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 604

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38

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46

&lt;210&gt; 616

&lt;211&gt; 1350

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 616

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&lt;211&gt; 449

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 617

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Cys Ser Gly Val Leu Val His Pro Gln Trp Val Leu Ser Ala Ala His
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Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu Gly Leu His Ser Leu Glu
 50          55          60
Ala Asp Gln Glu Pro Gly Ser Gln Met Val Glu Ala Ser Leu Ser Val
 65          70          75          80
Arg His Pro Glu Tyr Asn Arg Pro Leu Leu Ala Asn Asp Leu Met Leu
          85          90          95
Ile Lys Leu Asp Glu Ser Val Ser Glu Ser Asp Thr Ile Arg Ser Ile
          100          105          110
Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly Asn Ser Cys Leu Val Ser
          115          120          125
Gly Trp Gly Leu Leu Ala Asn Gly Arg Met Pro Thr Val Leu Gln Cys
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Val Asn Val Ser Val Val Ser Glu Glu Val Cys Ser Lys Leu Tyr Asp
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Pro Leu Tyr His Pro Ser Met Phe Cys Ala Gly Gly Gly Gln Asp Gln
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Lys Asp Ser Cys Asn Gly Asp Ser Gly Gly Pro Leu Ile Cys Asn Gly
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Tyr Leu Gln Gly Leu Val Ser Phe Gly Lys Ala Pro Cys Gly Gln Val
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His Ser Gln Pro Trp Gln Val Leu Val Ala Ser Arg Gly Arg Ala Val
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Cys Ile Arg Asn Lys Ser Val Ile Leu Leu Gly Arg His Ser Leu Phe
          275          280          285
His Pro Glu Asp Thr Gly Gln Val Phe Gln Val Ser His Ser Phe Pro
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His Pro Leu Tyr Asp Met Ser Leu Leu Lys Asn Arg Phe Leu Arg Pro
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Ala Glu Leu Thr Asp Ala Val Lys Val Met Asp Leu Pro Thr Gln Glu
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&lt;211&gt; 3674

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;400&gt; 619

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&lt;210&gt; 620

&lt;211&gt; 2051

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(2051)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 620

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&lt;210&gt; 621

&lt;211&gt; 2841

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(2841)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 621

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&lt;210&gt; 622

&lt;211&gt; 3228

&lt;212&gt; DNA

&lt;213&gt; Homo sapien

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(3228)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 622

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&lt;210&gt; 623

&lt;211&gt; 4894

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 623

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&lt;400&gt; 624

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&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 625

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&lt;213&gt; Homo sapiens

&lt;400&gt; 626

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&lt;210&gt; 627

&lt;211&gt; 123

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 627

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Ser Leu Val Met Asp Arg Leu Val Gln Arg Phe Gly Thr Arg Ala Val
          20              25              30

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Tyr Leu Ala Ser Val Ala Ala Phe Pro Val Ala Ala Gly Ala Thr Cys
          35              40              45

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Leu Ser His Ser Val Ala Val Val Thr Ala Ser Ala Ala Leu Thr Gly
          50              55              60

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Phe Thr Phe Ser Ala Leu Gln Ile Leu Pro Tyr Thr Leu Ala Ser Leu
          65              70              75              80

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Tyr His Arg Glu Lys Gln Val Leu Ile Gly Gln Trp Val Glu Ser Gly
          85              90              95

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239

Trp Glu Gly Trp Ser Gly Phe Leu Gly Gly Gln Leu Ala Gln Asn Leu  
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Val Ser Gly Lys Gln Leu Trp Arg Met Leu Leu  
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&lt;210&gt; 628

&lt;211&gt; 150

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 628

Met Val Gln Arg Leu Trp Val Ser Arg Leu Leu Arg His Arg Lys Ala  
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Gln Leu Leu Leu Val Asn Leu Leu Thr Phe Gly Leu Glu Val Cys Leu  
 20 25 30

Ala Ala Gly Ile Thr Tyr Val Pro Pro Leu Leu Leu Glu Val Gly Val  
 35 40 45

Glu Glu Lys Phe Met Thr Met Val Leu Gly Glu Ser Leu His Pro Pro  
 50 55 60

Ser Phe Leu Phe Gln Ile His Ala Thr Trp His Val Gly Gln Glu Tyr  
 65 70 75 80

Leu Cys Pro Gly Ser Cys Leu Glu Gly Glu Val Val Cys Trp Glu Gly  
 85 90 95

Ile Ala Gly Gln Glu Gly Asp Pro Gly Leu Arg Gly His Thr Lys Arg  
 100 105 110

Lys Lys Arg Ile Pro Arg Thr Tyr Pro Ser His Leu Trp Ile Pro Gly  
 115 120 125

Pro Ala Gln Ser Leu Ala His Arg Arg His Trp Arg Asn Ala Pro Asn  
 130 135 140

Leu Trp Leu Ala Leu Leu  
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&lt;210&gt; 629

&lt;211&gt; 371

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 629

Met Leu Phe Pro Ser Phe Ser Arg Ser Leu Val Pro Leu Pro Leu Ala  
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Leu Tyr Leu Ser Gln Pro Leu Thr His Thr Thr Ser Leu Leu Ala Gly  
 20 25 30

Ile Gly Pro Val Leu Gly Leu Val Cys Val Pro Leu Leu Gly Ser Ala  
 35 40 45

Ser Asp His Trp Arg Gly Arg Tyr Gly Arg Arg Arg Pro Phe Ile Trp  
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 Ala Leu Ser Leu Gly Ile Leu Leu Ser Leu Phe Leu Ile Pro Arg Ala  
 65 70 75 80  
 Gly Trp Leu Ala Gly Leu Leu Cys Pro Asp Pro Arg Pro Leu Glu Leu  
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 Cys Phe Thr Pro Leu Glu Ala Leu Leu Ser Asp Leu Phe Arg Asp Pro  
 115 120 125  
 Asp His Cys Arg Gln Ala Tyr Ser Val Tyr Ala Phe Met Ile Ser Leu  
 130 135 140  
 Gly Gly Cys Leu Gly Tyr Leu Leu Pro Ala Ile Asp Trp Asp Thr Ser  
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 Ala Leu Ala Pro Tyr Leu Gly Thr Gln Glu Glu Cys Leu Phe Gly Leu  
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 Glu Glu Ala Ala Leu Gly Pro Thr Glu Pro Ala Glu Gly Leu Ser Ala  
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 210 215 220  
 Arg Asn Leu Gly Ala Leu Leu Pro Arg Leu His Gln Leu Cys Cys Arg  
 225 230 235 240  
 Met Pro Arg Thr Leu Arg Arg Leu Phe Val Ala Glu Leu Cys Ser Trp  
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 Met Ala Leu Met Thr Phe Thr Leu Phe Tyr Thr Asp Phe Val Gly Glu  
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 Arg His Tyr Asp Glu Gly Lys Ala Leu Ala Ala Ser Arg Gly Trp Cys  
 290 295 300  
 Gly Ser Arg Pro Pro Glu Thr Thr Leu Gly Ala Val Ser Gly Leu Val  
 305 310 315 320  
 Pro Leu His Pro Gly Pro Asp Phe Ser Val Arg Lys Val Gly Met Asp  
 325 330 335  
 Pro Ile Cys Ile His Gly Phe Ser Trp Val Trp Asn Ile Ser Ala Cys  
 340 345 350

Gly Phe Arg Lys Ala Ser Gly Cys Ser Arg Ser Leu Ile Arg Val Val  
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Ala Pro Val  
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<210> 630

<211> 2983

<212> DNA

<213> Homo sapiens

<400> 630

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&lt;210&gt; 631

&lt;211&gt; 3064

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 631

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&lt;210&gt; 632

&lt;211&gt; 684

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 632

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Ser Pro Val Phe Arg Arg Gly Gln Val Phe His Leu Arg Leu Val Leu
          35                      40                      45

Asn Gln Pro Leu Gln Ser Tyr His Gln Leu Lys Leu Glu Phe Ser Thr
          50                      55                      60

Gly Pro Asn Pro Ser Ile Ala Lys His Thr Leu Val Val Leu Asp Pro
          65                      70                      75                      80

Arg Thr Pro Ser Asp His Tyr Asn Trp Gln Ala Thr Leu Gln Asn Glu
          85                      90                      95

Ser Gly Lys Glu Val Thr Val Ala Val Thr Ser Ser Pro Asn Ala Ile
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Leu Gly Lys Tyr Gln Leu Asn Val Lys Thr Gly Asn His Ile Leu Lys
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Ser Glu Glu Asn Ile Leu Tyr Leu Leu Phe Asn Pro Trp Cys Lys Glu
          130                      135                      140

Asp Met Val Phe Met Pro Asp Glu Asp Glu Arg Lys Glu Tyr Ile Leu
          145                      150                      155                      160

Asn Asp Thr Gly Cys His Tyr Val Gly Ala Ala Arg Ser Ile Lys Cys
          165                      170                      175

Lys Pro Trp Asn Phe Gly Gln Phe Glu Lys Asn Val Leu Asp Cys Cys
          180                      185                      190

Ile Ser Leu Leu Thr Glu Ser Ser Leu Lys Pro Thr Asp Arg Arg Asp
          195                      200                      205

Pro Val Leu Val Cys Arg Ala Met Cys Ala Met Met Ser Phe Glu Lys
          210                      215                      220

Gly Gln Gly Val Leu Ile Gly Asn Trp Thr Gly Asp Tyr Glu Gly Gly

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225		230		235		240									
Thr	Ala	Pro	Tyr	Lys	Trp	Thr	Gly	Ser	Ala	Pro	Ile	Leu	Gln	Gln	Tyr
				245					250					255	
Tyr	Asn	Thr	Lys	Gln	Ala	Val	Cys	Phe	Gly	Gln	Cys	Trp	Val	Phe	Ala
			260					265					270		
Gly	Ile	Leu	Thr	Thr	Val	Leu	Arg	Ala	Leu	Gly	Ile	Pro	Ala	Arg	Ser
		275					280					285			
Val	Thr	Gly	Phe	Asp	Ser	Ala	His	Asp	Thr	Glu	Arg	Asn	Leu	Thr	Val
		290				295					300				
Asp	Thr	Tyr	Val	Asn	Glu	Asn	Gly	Lys	Lys	Ile	Thr	Ser	Met	Thr	His
305					310					315					320
Asp	Ser	Val	Trp	Asn	Phe	His	Val	Trp	Thr	Asp	Ala	Trp	Met	Lys	Arg
				325					330					335	
Pro	Asp	Leu	Pro	Lys	Gly	Tyr	Asp	Gly	Trp	Gln	Ala	Val	Asp	Ala	Thr
			340					345					350		
Pro	Gln	Glu	Arg	Ser	Gln	Gly	Val	Phe	Cys	Cys	Gly	Pro	Ser	Pro	Leu
		355					360					365			
Thr	Ala	Ile	Arg	Lys	Gly	Asp	Ile	Phe	Ile	Val	Tyr	Asp	Thr	Arg	Phe
		370				375					380				
Val	Phe	Ser	Glu	Val	Asn	Gly	Asp	Arg	Leu	Ile	Trp	Leu	Val	Lys	Met
385					390					395					400
Val	Asn	Gly	Gln	Glu	Glu	Leu	His	Val	Ile	Ser	Met	Glu	Thr	Thr	Ser
				405					410					415	
Ile	Gly	Lys	Asn	Ile	Ser	Thr	Lys	Ala	Val	Gly	Gln	Asp	Arg	Arg	Arg
			420					425					430		
Asp	Ile	Thr	Tyr	Glu	Tyr	Lys	Tyr	Pro	Glu	Gly	Ser	Ser	Glu	Glu	Arg
		435					440					445			
Gln	Val	Met	Asp	His	Ala	Phe	Leu	Leu	Leu	Ser	Ser	Glu	Arg	Glu	His
		450				455					460				
Arg	Arg	Pro	Val	Lys	Glu	Asn	Phe	Leu	His	Met	Ser	Val	Gln	Ser	Asp
465					470					475					480
Asp	Val	Leu	Leu	Gly	Asn	Ser	Val	Asn	Phe	Thr	Val	Ile	Leu	Lys	Arg
				485					490					495	
Lys	Thr	Ala	Ala	Leu	Gln	Asn	Val	Asn	Ile	Leu	Gly	Ser	Phe	Glu	Leu
			500					505					510		
Gln	Leu	Tyr	Thr	Gly	Lys	Lys	Met	Ala	Lys	Leu	Cys	Asp	Leu	Asn	Lys
		515					520					525			
Thr	Ser	Gln	Ile	Gln	Gly	Gln	Val	Ser	Glu	Val	Thr	Leu	Thr	Leu	Asp
		530				535					540				

245

Ser Lys Thr Tyr Ile Asn Ser Leu Ala Ile Leu Asp Asp Glu Pro Val  
 545 550 555 560  
 Ile Arg Gly Phe Ile Ile Ala Glu Ile Val Glu Ser Lys Glu Ile Met  
 565 570 575  
 Ala Ser Glu Val Phe Thr Ser Phe Gln Tyr Pro Glu Phe Ser Ile Glu  
 580 585 590  
 Leu Pro Asn Thr Gly Arg Ile Gly Gln Leu Leu Val Cys Asn Cys Ile  
 595 600 605  
 Phe Lys Asn Thr Leu Ala Ile Pro Leu Thr Asp Val Lys Phe Ser Leu  
 610 615 620  
 Glu Ser Leu Gly Ile Ser Ser Leu Gln Thr Ser Asp His Gly Thr Val  
 625 630 635 640  
 Gln Pro Gly Glu Thr Ile Gln Ser Gln Ile Lys Cys Thr Pro Ile Lys  
 645 650 655  
 Thr Gly Pro Lys Lys Phe Ile Val Lys Leu Ser Ser Lys Gln Val Lys  
 660 665 670  
 Glu Ile Asn Ala Gln Lys Ile Val Leu Ile Thr Lys  
 675 680

&lt;210&gt; 633

&lt;211&gt; 679

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 633

Met Met Asp Ala Ser Lys Glu Leu Gln Val Leu His Ile Asp Phe Leu  
 5 10 15  
 Asn Gln Asp Asn Ala Val Ser His His Thr Trp Glu Phe Gln Thr Ser  
 20 25 30  
 Ser Pro Val Phe Arg Arg Gly Gln Val Phe His Leu Arg Leu Val Leu  
 35 40 45  
 Asn Gln Pro Leu Gln Ser Tyr His Gln Leu Lys Leu Glu Phe Ser Thr  
 50 55 60  
 Gly Pro Asn Pro Ser Ile Ala Lys His Thr Leu Val Val Leu Asp Pro  
 65 70 75 80  
 Arg Thr Pro Ser Asp His Tyr Asn Trp Gln Ala Thr Leu Gln Asn Glu  
 85 90 95  
 Ser Gly Lys Glu Val Thr Val Ala Val Thr Ser Ser Pro Asn Ala Ile  
 100 105 110  
 Leu Gly Lys Tyr Gln Leu Asn Val Lys Thr Gly Asn His Ile Leu Lys  
 115 120 125

Ser Glu Glu Asn Ile Leu Tyr Leu Leu Phe Asn Pro Trp Cys Lys Glu  
 130 135 140  
 Asp Met Val Phe Met Pro Asp Glu Asp Glu Arg Lys Glu Tyr Ile Leu  
 145 150 155 160  
 Asn Asp Thr Gly Cys His Tyr Val Gly Ala Ala Arg Ser Ile Lys Cys  
 165 170 175  
 Lys Pro Trp Asn Phe Gly Gln Phe Glu Lys Asn Val Leu Asp Cys Cys  
 180 185 190  
 Ile Ser Leu Leu Thr Glu Ser Ser Leu Lys Pro Thr Asp Arg Arg Asp  
 195 200 205  
 Pro Val Leu Val Cys Arg Ala Met Cys Ala Met Met Ser Phe Glu Lys  
 210 215 220  
 Gly Gln Gly Val Leu Ile Gly Asn Trp Thr Gly Asp Tyr Glu Gly Gly  
 225 230 235 240  
 Thr Ala Pro Tyr Lys Trp Thr Gly Ser Ala Pro Ile Leu Gln Gln Tyr  
 245 250 255  
 Tyr Asn Thr Lys Gln Ala Val Cys Phe Gly Gln Cys Trp Val Phe Ala  
 260 265 270  
 Gly Ile Leu Thr Thr Val Leu Arg Ala Leu Gly Ile Pro Ala Arg Ser  
 275 280 285  
 Val Thr Gly Phe Asp Ser Ala His Asp Thr Glu Arg Asn Leu Thr Val  
 290 295 300  
 Asp Thr Tyr Val Asn Glu Asn Gly Glu Lys Ile Thr Ser Met Thr His  
 305 310 315 320  
 Asp Ser Val Trp Asn Phe His Val Trp Thr Asp Ala Trp Met Lys Arg  
 325 330 335  
 Pro Tyr Asp Gly Trp Gln Ala Val Asp Ala Thr Pro Gln Glu Arg Ser  
 340 345 350  
 Gln Gly Val Phe Cys Cys Gly Pro Ser Pro Leu Thr Ala Ile Arg Lys  
 355 360 365  
 Gly Asp Ile Phe Ile Val Tyr Asp Thr Arg Phe Val Phe Ser Glu Val  
 370 375 380  
 Asn Gly Asp Arg Leu Ile Trp Leu Val Lys Met Val Asn Gly Gln Glu  
 385 390 395 400  
 Glu Leu His Val Ile Ser Met Glu Thr Thr Ser Ile Gly Lys Asn Ile  
 405 410 415  
 Ser Thr Lys Ala Val Gly Gln Asp Arg Arg Arg Asp Ile Thr Tyr Glu  
 420 425 430  
 Tyr Lys Tyr Pro Glu Gly Ser Ser Glu Glu Arg Gln Val Met Asp His

435	440	445
Ala Phe Leu Leu Leu Ser Ser Glu Arg Glu His Arg Gln Pro Val Lys		
450	455	460
Glu Asn Phe Leu His Met Ser Val Gln Ser Asp Asp Val Leu Leu Gly		
465	470	475
Asn Ser Val Asn Phe Thr Val Ile Leu Lys Arg Lys Thr Ala Ala Leu		
485	490	495
Gln Asn Val Asn Ile Leu Gly Ser Phe Glu Leu Gln Leu Tyr Thr Gly		
500	505	510
Lys Lys Met Ala Lys Leu Cys Asp Leu Asn Lys Thr Ser Gln Ile Gln		
515	520	525
Gly Gln Val Ser Glu Val Thr Leu Thr Leu Asp Ser Lys Thr Tyr Ile		
530	535	540
Asn Ser Leu Ala Ile Leu Asp Asp Glu Pro Val Ile Arg Gly Phe Ile		
545	550	555
Ile Ala Glu Ile Val Glu Ser Lys Glu Ile Met Ala Ser Glu Val Phe		
565	570	575
Thr Ser Asn Gln Tyr Pro Glu Phe Ser Ile Glu Leu Pro Asn Thr Gly		
580	585	590
Arg Ile Gly Gln Leu Leu Val Cys Asn Cys Ile Phe Lys Asn Thr Leu		
595	600	605
Ala Ile Pro Leu Thr Asp Val Lys Phe Ser Leu Glu Ser Leu Gly Ile		
610	615	620
Ser Ser Leu Gln Thr Ser Asp His Gly Thr Val Gln Pro Gly Glu Thr		
625	630	635
Ile Gln Ser Gln Ile Lys Cys Thr Pro Ile Lys Thr Gly Pro Lys Lys		
645	650	655
Phe Ile Val Lys Leu Ser Ser Lys Gln Val Lys Glu Ile Asn Ala Gln		
660	665	670
Lys Ile Val Leu Ile Thr Lys		
675		

&lt;210&gt; 634

&lt;211&gt; 5668

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 634

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tacagtgaag gcgacttggt gaattttatt caagcaaatt ttaagaaacg agaatgtgtc 180

ttctttacca	aagattccaa	ggccacggag	aatgtgtgca	agtgtggcta	tgcccagagc	240
cagcacatgg	aaggcaccce	gatcaaccaa	agtgagaaat	ggaactacaa	gaaacacacc	300
aaggaatttc	ctaccgacgc	ctttggggat	attcagtttg	agacactggg	gaagaaaggg	360
aagtatatac	gtctgtcctg	cgacacggac	gcggaaatcc	tttacgagct	gctgacccag	420
cactggcacc	tgaaaacacc	caacctggtc	atttctgtga	ccggggggcg	caagaacttc	480
gcctgaagc	cgcgcacgcg	caagatcttc	agccggctca	tctacatcgc	gcagtccaaa	540
ggtgcttgga	ttctcacggg	aggcaccat	tatggcctga	cgaagtacat	cggggaggtg	600
gtgagagata	acaccatcag	caggagtcca	gaggagaata	ttgtggccat	tgccatagca	660
gcttggggca	tggtctccaa	ccgggacacc	ctcatcagga	attgcgatgc	tgagggctat	720
tttttagccc	agtaccttat	ggatgacttc	acaagggatc	cactgtatat	cctggacaac	780
aaccacacac	atttgcctgt	cgtggacaat	ggtgtcatg	gacatcccac	tgctgaagca	840
aagctccgga	atcagctaga	gaagcatatc	tctgagcgca	ctattcaaga	ttccaactat	900
ggtggcaaga	tccccattgt	gtgttttgcc	caaggagggtg	gaaaagagac	tttgaaagcc	960
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accatcccc	tgggtgtcat	ctacatgtta	tccaccaaca	tcctgctggt	caacctgctg	2940
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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 5668

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&lt;210&gt; 635

&lt;211&gt; 1095

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 635

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Met Arg Asn Arg Arg Asn Asp Thr Leu Asp Ser Thr Arg Thr Leu Tyr
      5              10              15

Ser Ser Ala Ser Arg Ser Thr Asp Leu Ser Tyr Ser Glu Ser Asp Leu
      20              25              30

Val Asn Phe Ile Gln Ala Asn Phe Lys Lys Arg Glu Cys Val Phe Phe
      35              40              45

Thr Lys Asp Ser Lys Ala Thr Glu Asn Val Cys Lys Cys Gly Tyr Ala
      50              55              60

Gln Ser Gln His Met Glu Gly Thr Gln Ile Asn Gln Ser Glu Lys Trp
      65              70              75              80

Asn Tyr Lys Lys His Thr Lys Glu Phe Pro Thr Asp Ala Phe Gly Asp
      85              90              95

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Ile Gln Phe Glu Thr Leu Gly Lys Lys Gly Lys Tyr Ile Arg Leu Ser  
 100 105 110  
 Cys Asp Thr Asp Ala Glu Ile Leu Tyr Glu Leu Leu Thr Gln His Trp  
 115 120 125  
 His Leu Lys Thr Pro Asn Leu Val Ile Ser Val Thr Gly Gly Ala Lys  
 130 135 140  
 Asn Phe Ala Leu Lys Pro Arg Met Arg Lys Ile Phe Ser Arg Leu Ile  
 145 150 155 160  
 Tyr Ile Ala Gln Ser Lys Gly Ala Trp Ile Leu Thr Gly Gly Thr His  
 165 170 175  
 Tyr Gly Leu Thr Lys Tyr Ile Gly Glu Val Val Arg Asp Asn Thr Ile  
 180 185 190  
 Ser Arg Ser Ser Glu Glu Asn Ile Val Ala Ile Gly Ile Ala Ala Trp  
 195 200 205  
 Gly Met Val Ser Asn Arg Asp Thr Leu Ile Arg Asn Cys Asp Ala Glu  
 210 215 220  
 Gly Tyr Phe Leu Ala Gln Tyr Leu Met Asp Asp Phe Thr Arg Asp Pro  
 225 230 235 240  
 Leu Tyr Ile Leu Asp Asn Asn His Thr His Leu Leu Leu Val Asp Asn  
 245 250 255  
 Gly Cys His Gly His Pro Thr Val Glu Ala Lys Leu Arg Asn Gln Leu  
 260 265 270  
 Glu Lys His Ile Ser Glu Arg Thr Ile Gln Asp Ser Asn Tyr Gly Gly  
 275 280 285  
 Lys Ile Pro Ile Val Cys Phe Ala Gln Gly Gly Gly Lys Glu Thr Leu  
 290 295 300  
 Lys Ala Ile Asn Thr Ser Ile Lys Asn Lys Ile Pro Cys Val Val Val  
 305 310 315 320  
 Glu Gly Ser Gly Arg Ile Ala Asp Val Ile Ala Ser Leu Val Glu Val  
 325 330 335  
 Glu Asp Ala Pro Thr Ser Ser Ala Val Lys Glu Lys Leu Val Arg Phe  
 340 345 350  
 Leu Pro Arg Thr Val Ser Arg Leu Ser Glu Glu Glu Thr Glu Ser Trp  
 355 360 365  
 Ile Lys Trp Leu Lys Glu Ile Leu Glu Cys Ser His Leu Leu Thr Val  
 370 375 380  
 Ile Lys Met Glu Glu Ala Gly Asp Glu Ile Val Ser Asn Ala Ile Ser  
 385 390 395 400

Tyr Ala Leu Tyr Lys Ala Phe Ser Thr Ser Glu Gln Asp Lys Asp Asn  
 405 410 415  
 Trp Asn Gly Gln Leu Lys Leu Leu Leu Glu Trp Asn Gln Leu Asp Leu  
 420 425 430  
 Ala Asn Asp Glu Ile Phe Thr Asn Asp Arg Arg Trp Glu Ser Ala Asp  
 435 440 445  
 Leu Gln Glu Val Met Phe Thr Ala Leu Ile Lys Asp Arg Pro Lys Phe  
 450 455 460  
 Val Arg Leu Phe Leu Glu Asn Gly Leu Asn Leu Arg Lys Phe Leu Thr  
 465 470 475 480  
 His Asp Val Leu Thr Glu Leu Phe Ser Asn His Phe Ser Thr Leu Val  
 485 490 495  
 Tyr Arg Asn Leu Gln Ile Ala Lys Asn Ser Tyr Asn Asp Ala Leu Leu  
 500 505 510  
 Thr Phe Val Trp Lys Leu Val Ala Asn Phe Arg Arg Gly Phe Arg Lys  
 515 520 525  
 Glu Asp Arg Asn Gly Arg Asp Glu Met Asp Ile Glu Leu His Asp Val  
 530 535 540  
 Ser Pro Ile Thr Arg His Pro Leu Gln Ala Leu Phe Ile Trp Ala Ile  
 545 550 555 560  
 Leu Gln Asn Lys Lys Glu Leu Ser Lys Val Ile Trp Glu Gln Thr Arg  
 565 570 575  
 Gly Cys Thr Leu Ala Ala Leu Gly Ala Ser Lys Leu Leu Lys Thr Leu  
 580 585 590  
 Ala Lys Val Lys Asn Asp Ile Asn Ala Ala Gly Glu Ser Glu Glu Leu  
 595 600 605  
 Ala Asn Glu Tyr Glu Thr Arg Ala Val Glu Leu Phe Thr Glu Cys Tyr  
 610 615 620  
 Ser Ser Asp Glu Asp Leu Ala Glu Gln Leu Leu Val Tyr Ser Cys Glu  
 625 630 635 640  
 Ala Trp Gly Gly Ser Asn Cys Leu Glu Leu Ala Val Glu Ala Thr Asp  
 645 650 655  
 Gln His Phe Thr Ala Gln Pro Gly Val Gln Asn Phe Leu Ser Lys Gln  
 660 665 670  
 Trp Tyr Gly Glu Ile Ser Arg Asp Thr Lys Asn Trp Lys Ile Ile Leu  
 675 680 685  
 Cys Leu Phe Ile Ile Pro Leu Val Gly Cys Gly Phe Val Ser Phe Arg  
 690 695 700  
 Lys Lys Pro Val Asp Lys His Lys Lys Leu Leu Trp Tyr Tyr Val Ala



705		710		715		720
Phe Phe Thr Ser Pro Phe Val Val Phe Ser Trp Asn Val Val Phe Tyr						
		725		730		735
Ile Ala Phe Leu Leu Leu Phe Ala Tyr Val Leu Leu Met Asp Phe His						
		740		745		750
Ser Val Pro His Pro Pro Glu Leu Val Leu Tyr Ser Leu Val Phe Val						
		755		760		765
Leu Phe Cys Asp Glu Val Arg Gln Trp Tyr Val Asn Gly Val Asn Tyr						
		770		775		780
Phe Thr Asp Leu Trp Asn Val Met Asp Thr Leu Gly Leu Phe Tyr Phe						
		785		790		795
Ile Ala Gly Ile Val Phe Arg Leu His Ser Ser Asn Lys Ser Ser Leu						
		805		810		815
Tyr Ser Gly Arg Val Ile Phe Cys Leu Asp Tyr Ile Ile Phe Thr Leu						
		820		825		830
Arg Leu Ile His Ile Phe Thr Val Ser Arg Asn Leu Gly Pro Lys Ile						
		835		840		845
Ile Met Leu Gln Arg Met Leu Ile Asp Val Phe Phe Phe Leu Phe Leu						
		850		855		860
Phe Ala Val Trp Met Val Ala Phe Gly Val Ala Arg Gln Gly Ile Leu						
		865		870		875
Arg Gln Asn Glu Gln Arg Trp Arg Trp Ile Phe Arg Ser Val Ile Tyr						
		885		890		895
Glu Pro Tyr Leu Ala Met Phe Gly Gln Val Pro Ser Asp Val Asp Gly						
		900		905		910
Thr Thr Tyr Asp Phe Ala His Cys Thr Phe Thr Gly Asn Glu Ser Lys						
		915		920		925
Pro Leu Cys Val Glu Leu Asp Glu His Asn Leu Pro Arg Phe Pro Glu						
		930		935		940
Trp Ile Thr Ile Pro Leu Val Cys Ile Tyr Met Leu Ser Thr Asn Ile						
		945		950		955
Leu Leu Val Asn Leu Leu Val Ala Met Phe Gly Tyr Thr Val Gly Thr						
		965		970		975
Val Gln Glu Asn Asn Asp Gln Val Trp Lys Phe Gln Arg Tyr Phe Leu						
		980		985		990
Val Gln Glu Tyr Cys Ser Arg Leu Asn Ile Pro Phe Pro Phe Ile Val						
		995		1000		1005
Phe Ala Tyr Phe Tyr Met Val Val Lys Lys Cys Phe Lys Cys Cys Cys						
		1010		1015		1020

Lys Glu Lys Asn Met Glu Ser Ser Val Cys Cys Phe Lys Asn Glu Asp  
 1025 1030 1035 1040  
 Asn Glu Thr Leu Ala Trp Glu Gly Val Met Lys Glu Asn Tyr Leu Val  
 1045 1050 1055  
 Lys Ile Asn Thr Lys Ala Asn Asp Thr Ser Glu Glu Met Arg His Arg  
 1060 1065 1070  
 Phe Arg Gln Leu Asp Thr Lys Leu Asn Asp Leu Lys Gly Leu Leu Lys  
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&lt;210&gt; 636

&lt;211&gt; 3639

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 636

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&lt;210&gt; 637

&lt;211&gt; 1095

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; VARIANT

&lt;222&gt; (1)...(1095)

&lt;223&gt; Xaa = Any Amino Acid

&lt;400&gt; 637

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Met Arg Asn Arg Arg Asn Asp Thr Leu Asp Ser Thr Arg Thr Leu Tyr
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Ser Ser Ala Ser Arg Ser Thr Asp Leu Ser Tyr Ser Glu Ser Asp Leu
      20              25              30

Val Asn Phe Ile Gln Ala Asn Phe Lys Lys Arg Glu Cys Val Phe Phe
      35              40              45

Thr Lys Asp Ser Lys Ala Thr Glu Asn Val Cys Lys Cys Gly Tyr Ala
      50              55              60

Gln Ser Gln His Met Glu Gly Thr Gln Ile Asn Gln Ser Glu Lys Trp
      65              70              75              80

Asn Tyr Lys Lys His Thr Lys Glu Phe Pro Thr Asp Ala Phe Gly Asp
      85              90              95

Ile Gln Phe Glu Thr Leu Gly Lys Lys Gly Lys Tyr Ile Arg Leu Ser

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100					105					110					
Cys	Asp	Thr	Asp	Ala	Glu	Ile	Leu	Tyr	Glu	Leu	Leu	Thr	Gln	His	Trp
	115						120					125			
His	Leu	Lys	Thr	Pro	Asn	Leu	Val	Ile	Ser	Val	Thr	Gly	Gly	Ala	Lys
	130					135					140				
Asn	Phe	Ala	Leu	Lys	Pro	Arg	Met	Arg	Lys	Ile	Phe	Ser	Arg	Leu	Ile
145					150					155					160
Tyr	Ile	Ala	Gln	Ser	Lys	Gly	Ala	Trp	Ile	Leu	Thr	Gly	Gly	Thr	His
				165					170						175
Tyr	Gly	Leu	Met	Lys	Tyr	Ile	Gly	Glu	Val	Val	Arg	Asp	Asn	Thr	Ile
			180					185					190		
Ser	Arg	Ser	Ser	Glu	Glu	Asn	Ile	Val	Ala	Ile	Gly	Ile	Ala	Ala	Trp
		195					200					205			
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Gly	Tyr	Phe	Leu	Ala	Gln	Tyr	Leu	Met	Asp	Asp	Phe	Thr	Arg	Asp	Pro
225					230					235					240
Leu	Tyr	Ile	Leu	Asp	Asn	Asn	His	Thr	His	Leu	Leu	Leu	Val	Asp	Asn
				245					250					255	
Gly	Cys	His	Gly	His	Pro	Thr	Val	Glu	Ala	Lys	Leu	Arg	Asn	Gln	Leu
			260					265					270		
Glu	Lys	Tyr	Ile	Ser	Glu	Arg	Thr	Ile	Gln	Asp	Ser	Asn	Tyr	Gly	Gly
		275					280					285			
Lys	Ile	Pro	Ile	Val	Cys	Phe	Ala	Gln	Gly	Gly	Gly	Lys	Glu	Thr	Leu
	290					295					300				
Lys	Ala	Ile	Asn	Thr	Ser	Ile	Lys	Asn	Lys	Ile	Pro	Cys	Val	Val	Val
305					310					315					320
Glu	Gly	Ser	Gly	Gln	Ile	Ala	Asp	Val	Ile	Ala	Ser	Leu	Val	Glu	Val
				325					330					335	
Glu	Asp	Ala	Leu	Thr	Ser	Ser	Ala	Val	Lys	Glu	Lys	Leu	Val	Arg	Phe
			340					345						350	
Leu	Pro	Arg	Thr	Val	Ser	Arg	Leu	Pro	Glu	Glu	Glu	Thr	Glu	Ser	Trp
		355					360					365			
Ile	Lys	Trp	Leu	Lys	Glu	Ile	Leu	Glu	Cys	Ser	His	Leu	Leu	Thr	Val
	370					375					380				
Ile	Lys	Met	Glu	Glu	Ala	Gly	Asp	Glu	Ile	Val	Ser	Asn	Ala	Ile	Ser
385					390					395					400
Tyr	Ala	Leu	Tyr	Lys	Ala	Phe	Ser	Thr	Ser	Glu	Gln	Asp	Lys	Asp	Asn
				405					410					415	

Trp Asn Gly Gln Leu Lys Leu Leu Leu Glu Trp Asn Gln Leu Asp Leu  
 420 425 430  
 Ala Asn Asp Glu Ile Phe Thr Asn Asp Arg Arg Trp Glu Ser Ala Asp  
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 Leu Gln Glu Val Met Phe Thr Ala Leu Ile Lys Asp Arg Pro Lys Phe  
 450 455 460  
 Val Arg Leu Phe Leu Glu Asn Gly Leu Asn Leu Arg Lys Phe Leu Thr  
 465 470 475 480  
 His Asp Val Leu Thr Glu Leu Phe Ser Asn His Phe Ser Thr Leu Val  
 485 490 495  
 Tyr Arg Asn Leu Gln Ile Ala Lys Asn Ser Tyr Asn Asp Ala Leu Leu  
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 Thr Phe Val Trp Lys Leu Val Ala Asn Phe Arg Arg Gly Phe Arg Lys  
 515 520 525  
 Glu Asp Arg Asn Gly Arg Asp Glu Met Asp Ile Glu Leu His Asp Val  
 530 535 540  
 Ser Pro Ile Thr Arg His Pro Leu Gln Ala Leu Phe Ile Trp Ala Ile  
 545 550 555 560  
 Leu Gln Asn Lys Lys Glu Leu Ser Lys Val Ile Trp Glu Gln Thr Arg  
 565 570 575  
 Gly Cys Thr Leu Ala Ala Leu Gly Ala Ser Lys Leu Leu Lys Thr Leu  
 580 585 590  
 Ala Lys Val Lys Asn Asp Ile Asn Ala Ala Gly Glu Ser Glu Glu Leu  
 595 600 605  
 Ala Asn Glu Tyr Glu Thr Arg Ala Val Glu Leu Phe Thr Glu Cys Tyr  
 610 615 620  
 Ser Ser Asp Glu Asp Leu Ala Glu Gln Leu Leu Val Tyr Ser Cys Glu  
 625 630 635 640  
 Ala Trp Gly Gly Ser Asn Cys Leu Glu Leu Ala Val Glu Ala Thr Asp  
 645 650 655  
 Gln His Phe Ile Ala Gln Pro Gly Val Gln Asn Phe Leu Ser Lys Gln  
 660 665 670  
 Trp Tyr Gly Glu Ile Ser Arg Asp Thr Lys Asn Trp Lys Ile Ile Leu  
 675 680 685  
 Cys Leu Phe Ile Ile Pro Leu Val Gly Cys Gly Phe Val Ser Phe Arg  
 690 695 700  
 Lys Lys Pro Val Asp Lys His Lys Lys Leu Leu Trp Tyr Tyr Val Ala  
 705 710 715 720

Phe Phe Thr Ser Pro Phe Val Val Phe Ser Trp Asn Val Val Phe Tyr  
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 Ile Ala Phe Leu Leu Leu Phe Ala Tyr Val Leu Leu Met Asp Phe His  
 740 745 750  
 Ser Val Pro His Pro Pro Glu Leu Val Leu Tyr Ser Leu Val Phe Val  
 755 760 765  
 Leu Phe Cys Asp Glu Val Arg Gln Trp Tyr Val Asn Gly Val Asn Tyr  
 770 775 780  
 Phe Thr Asp Leu Trp Asn Val Met Asp Thr Leu Gly Leu Phe Tyr Phe  
 785 790 795 800  
 Ile Ala Gly Ile Val Phe Arg Leu His Ser Ser Asn Lys Ser Ser Leu  
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 Tyr Ser Gly Arg Val Ile Phe Cys Leu Asp Tyr Ile Ile Phe Thr Leu  
 820 825 830  
 Arg Leu Ile His Ile Phe Thr Val Ser Arg Asn Leu Gly Pro Lys Ile  
 835 840 845  
 Ile Met Leu Gln Arg Met Leu Ile Asp Val Phe Phe Phe Leu Phe Leu  
 850 855 860  
 Phe Ala Xaa Trp Met Val Ala Phe Gly Val Ala Arg Gln Gly Ile Leu  
 865 870 875 880  
 Arg Gln Asn Glu Gln Arg Trp Arg Trp Ile Phe Arg Ser Val Ile Tyr  
 885 890 895  
 Glu Pro Tyr Leu Ala Met Phe Gly Gln Val Pro Ser Asp Val Asp Gly  
 900 905 910  
 Thr Thr Tyr Asp Phe Ala His Cys Thr Phe Thr Gly Asn Glu Ser Lys  
 915 920 925  
 Pro Leu Cys Val Glu Leu Asp Glu His Asn Leu Pro Arg Phe Pro Glu  
 930 935 940  
 Trp Ile Thr Ile Pro Leu Val Cys Ile Tyr Met Leu Ser Thr Asn Ile  
 945 950 955 960  
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 965 970 975  
 Val Gln Glu Asn Asn Asp Gln Val Trp Lys Phe Gln Arg Tyr Phe Leu  
 980 985 990  
 Val Gln Glu Tyr Cys Ser Arg Leu Asn Ile Pro Phe Pro Phe Ile Val  
 995 1000 1005  
 Phe Ala Tyr Phe Tyr Met Val Val Lys Lys Cys Phe Lys Cys Cys Cys  
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 Lys Glu Lys Asn Met Glu Ser Ser Val Cys Cys Phe Lys Asn Glu Asp

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1045	1050	1055	
Lys Ile Asn Thr Lys Ala Asn Asp Thr Ser Glu Glu Met Arg His Arg			
1060	1065	1070	
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<210> 657  
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&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 657

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&lt;210&gt; 658

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 658

Gly	Leu	His	Ser	Leu	Glu	Ala	Asp	Gln	Glu	Pro	Gly	Ser	Gln	Met
				5					10					15

&lt;210&gt; 659

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 659

Tyr	Thr	Ile	Gly	Leu	Gly	Leu	His	Ser	Leu	Glu	Ala	Asp	Gln	Glu
				5					10					15

&lt;210&gt; 660

&lt;211&gt; 14

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 660

Phe	Gln	Asn	Ser	Tyr	Thr	Ile	Gly	Leu	Gly	Leu	His	Ser	Leu
				5					10				

&lt;210&gt; 661

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 661

Leu	Ser	Ala	Ala	His	Cys	Phe	Gln	Asn	Ser	Tyr	Thr	Ile	Gly	Leu
				5					10					15

&lt;210&gt; 662

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 662

His	Pro	Gln	Trp	Val	Leu	Ser	Ala	Ala	His	Cys	Phe	Gln	Asn	Ser
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Ser

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<210> 668  
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&lt;400&gt; 668

Ser Val Ser Glu Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser  
5 10 15

&lt;210&gt; 669

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 669

Ile Lys Leu Asp Glu Ser Val Ser Glu Ser Asp Thr Ile Arg Ser  
5 10 15

&lt;210&gt; 670

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 670

Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser  
5 10 15

&lt;210&gt; 671

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 671

Arg Pro Leu Leu Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu  
5 10 15

&lt;210&gt; 672

&lt;211&gt; 35

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; PCR primer

&lt;400&gt; 672

ggaccagcat atgaggaaca gaaggaatga cactc

35

&lt;210&gt; 673

&lt;211&gt; 29

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; PCR primer

&lt;400&gt; 673

ccgctcgagt ccacccaag cttcacagg

29

```
<210> 675
<211> 652
<212> PRT
<213> Homo sapiens
```

```

<400> 675
Met Arg Asn Arg Arg Asn Asp Thr Leu Asp Ser Thr Arg Thr Leu Tyr
                    5                      10                      15

Ser Ser Ala Ser Arg Ser Thr Asp Leu Ser Tyr Ser Glu Ser Asp Leu
                20                      25                      30

Val Asn Phe Ile Gln Ala Asn Phe Lys Lys Arg Glu Cys Val Phe Phe
                35                      40                      45

Thr Lys Asp Ser Lys Ala Thr Glu Asn Val Cys Lys Cys Gly Tyr Ala
    50                      55                      60

```

Gln Ser Gln His Met Glu Gly Thr Gln Ile Asn Gln Ser Glu Lys Trp  
 65 70 75 80  
 Asn Tyr Lys Lys His Thr Lys Glu Phe Pro Thr Asp Ala Phe Gly Asp  
 85 90 95  
 Ile Gln Phe Glu Thr Leu Gly Lys Lys Gly Lys Tyr Ile Arg Leu Ser  
 100 105 110  
 Cys Asp Thr Asp Ala Glu Ile Leu Tyr Glu Leu Leu Thr Gln His Trp  
 115 120 125  
 His Leu Lys Thr Pro Asn Leu Val Ile Ser Val Thr Gly Gly Ala Lys  
 130 135 140  
 Asn Phe Ala Leu Lys Pro Arg Met Arg Lys Ile Phe Ser Arg Leu Ile  
 145 150 155 160  
 Tyr Ile Ala Gln Ser Lys Gly Ala Trp Ile Leu Thr Gly Gly Thr His  
 165 170 175  
 Tyr Gly Leu Met Lys Tyr Ile Gly Glu Val Val Arg Asp Asn Thr Ile  
 180 185 190  
 Ser Arg Ser Ser Glu Glu Asn Ile Val Ala Ile Gly Ile Ala Ala Trp  
 195 200 205  
 Gly Met Val Ser Asn Arg Asp Thr Leu Ile Arg Asn Cys Asp Ala Glu  
 210 215 220  
 Gly Tyr Phe Leu Ala Gln Tyr Leu Met Asp Asp Phe Thr Arg Asp Pro  
 225 230 235 240  
 Leu Tyr Ile Leu Asp Asn Asn His Thr His Leu Leu Leu Val Asp Asn  
 245 250 255  
 Gly Cys His Gly His Pro Thr Val Glu Ala Lys Leu Arg Asn Gln Leu  
 260 265 270  
 Glu Lys Tyr Ile Ser Glu Arg Thr Ile Gln Asp Ser Asn Tyr Gly Gly  
 275 280 285  
 Lys Ile Pro Ile Val Cys Phe Ala Gln Gly Gly Gly Lys Glu Thr Leu  
 290 295 300  
 Lys Ala Ile Asn Thr Ser Ile Lys Asn Lys Ile Pro Cys Val Val Val  
 305 310 315 320  
 Glu Gly Ser Gly Gln Ile Ala Asp Val Ile Ala Ser Leu Val Glu Val  
 325 330 335  
 Glu Asp Ala Leu Thr Ser Ser Ala Val Lys Glu Lys Leu Val Arg Phe  
 340 345 350  
 Leu Pro Arg Thr Val Ser Arg Leu Pro Glu Glu Glu Thr Glu Ser Trp  
 355 360 365  
 Ile Lys Trp Leu Lys Glu Ile Leu Glu Cys Ser His Leu Leu Thr Val

370	375	380
Ile Lys Met Glu Glu Ala Gly Asp Glu Ile Val Ser Asn Ala Ile Ser		
385	390	395 400
Tyr Ala Leu Tyr Lys Ala Phe Ser Thr Ser Glu Gln Asp Lys Asp Asn		
	405	410 415
Trp Asn Gly Gln Leu Lys Leu Leu Leu Glu Trp Asn Gln Leu Asp Leu		
	420	425 430
Ala Asn Asp Glu Ile Phe Thr Asn Asp Arg Arg Trp Glu Ser Ala Asp		
	435	440 445
Leu Gln Glu Val Met Phe Thr Ala Leu Ile Lys Asp Arg Pro Lys Phe		
	450	455 460
Val Arg Leu Phe Leu Glu Asn Gly Leu Asn Leu Arg Lys Phe Leu Thr		
	465	470 475 480
His Asp Val Leu Thr Glu Leu Phe Ser Asn His Phe Ser Thr Leu Val		
	485	490 495
Tyr Arg Asn Leu Gln Ile Ala Lys Asn Ser Tyr Asn Asp Ala Leu Leu		
	500	505 510
Thr Phe Val Trp Lys Leu Val Ala Asn Phe Arg Arg Gly Phe Arg Lys		
	515	520 525
Glu Asp Arg Asn Gly Arg Asp Glu Met Asp Ile Glu Leu His Asp Val		
	530	535 540
Ser Pro Ile Thr Arg His Pro Leu Gln Ala Leu Phe Ile Trp Ala Ile		
	545	550 555 560
Leu Gln Asn Lys Lys Glu Leu Ser Lys Val Ile Trp Glu Gln Thr Arg		
	565	570 575
Gly Cys Thr Leu Ala Ala Leu Gly Ala Ser Lys Leu Leu Lys Thr Leu		
	580	585 590
Ala Lys Val Lys Asn Asp Ile Asn Ala Ala Gly Glu Ser Glu Glu Leu		
	595	600 605
Ala Asn Glu Tyr Glu Thr Arg Ala Val Glu Leu Phe Thr Glu Cys Tyr		
	610	615 620
Ser Ser Asp Glu Asp Leu Ala Glu Gln Leu Leu Val Tyr Ser Cys Glu		
	625	630 635 640
Ala Trp Gly Gly Leu Glu His His His His His His		
	645	650

&lt;210&gt; 676

&lt;211&gt; 132

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 676

```

Thr Ala Ala Ser Asp Asn Phe Gln Leu Ser Gln Gly Gly Gln Gly Phe
1           5           10           15
Ala Ile Pro Ile Gly Gln Ala Met Ala Ile Ala Gly Gln Ile Arg Ser
          20           25           30
Gly Gly Gly Ser Pro Thr Val His Ile Gly Pro Thr Ala Phe Leu Gly
          35           40           45
Leu Gly Val Val Asp Asn Asn Gly Asn Gly Ala Arg Val Gln Arg Val
          50           55           60
Val Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr Gly Asp Val
65           70           75           80
Ile Thr Ala Val Asp Gly Ala Pro Ile Asn Ser Ala Thr Ala Met Ala
          85           90           95
Asp Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser Val Asn Trp
          100          105          110
Gln Thr Lys Ser Gly Gly Thr Arg Thr Gly Asn Val Thr Leu Ala Glu
          115          120          125
Gly Pro Pro Ala
          130

```

&lt;210&gt; 677

&lt;211&gt; 36

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; PCR primer

&lt;400&gt; 677

ggggaattca tgatccggga gaaatttgcc cactgc

36

&lt;210&gt; 678

&lt;211&gt; 33

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; PCR primer

&lt;400&gt; 678

gggctcgagt caggagtttg agaccagcct ggc

33

&lt;210&gt; 679

&lt;211&gt; 675

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 679

```

atgcatcacc atcaccatca cacggccgcg tccgataact tccagctgtc ccagggtggg 60
cagggtattcg ccattccgat cgggcaggcg atggcgatcg cgggccagat caagcttccc 120

```



```

accgttcata tcgggcctac cgccttcctc ggcttgggtg ttgtcgacaa caacggcaac 180
ggcgacacgag tccaacgcgt ggtcgggagc gctccggcgg caagtctcgg catctccacc 240
ggcgacgtga tcaccgcggt cgacggcgct ccgatcaact cggccaccgc gatggcggac 300
gcgcttaacg ggcatcatcc cggtgacgtc atctcgggtga cctggcaaac caagtccggc 360
ggcacgcgta cagggaaacgt gacattggcc gagggacccc cggccgaatt catgatccgg 420
gagaaatttg cccactgcac cgtgctaacc attgcacaca gattgaacac cattattgac 480
agcgacaaga taatgggttt agattcagga agactgaaag aatatgatga gccgtatggt 540
ttgctgcaaa ataaagagag cctattttac aagatgggtg aacaactggg caaggcagaa 600
gccgctgccc tcactgaaac agcaaaacag agatgggggt tcaccatggt gccaggctg 660
gtctcaaact cctga                                     675

```

&lt;210&gt; 680

&lt;211&gt; 291

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 680

```

atgggggatcc gggagaaatt tgcccactgc accgtgctaa ccattgcaca cagattgaac 60
accattattg acagcgacaa gataatgggt ttagattcag gaagactgaa agaatatgat 120
gagccgtatg ttttgcctga aaataaagag agcctatttt acaagatggt gcaacaactg 180
ggcaaggcag aagccgctgc cctcactgaa acagcaaaac agagatgggg ttccaccatg 240
ttggccaggc tgggtctcaa ctccctcgag caccaccacc accaccactg a 291

```

&lt;210&gt; 681

&lt;211&gt; 1074

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 681

```

atgtcagcca ttgagaggggt gtcagaggca atcgtcagca tccgaagaat ccagaccttt 60
ttgctacttg atgagatata acagcgcaac cgtcagctgc cgtcagatgg taaaaagatg 120
gtgcatgtgc aggattttac tgcttttttg gataaggcat cagagacccc aactctacaa 180
ggcctttcct ttactgtcag acctggcgaa ttgttagctg tggtcggccc cgtgggagca 240
gggaagtcat cactgttaag tgccgtgctc ggggaattgg cccaagtca cgggctggtc 300
agcgtgcatg gaagaattgc ctatgtgtct cagcagccct ggggtgtctc gggaactctg 360
aggagtaata ttttatttgg gaagaaatac gaaaaggaaac gatatgaaaa agtcataaag 420
gcttgtgtctc tgaaaaagga tttacagctg ttggaggatg gtgatctgac tgtgatagga 480
gatcggggaa ccacgctgag tggagggcag aaagcacggg taaaccttgc aagagcagtg 540
tatcaagatg ctgacatcta tctcctggac gatcctctca gtgcagtaga tgcggaagtt 600
agcagacact tgttcgaact gtgtatttgt caaattttgc atgagaagat cacaatttta 660
gtgactcatc agttgcagta cctcaaagct gcaagtcaga ttctgatatt gaaagatggt 720
aaaaatgggtc agaaggggac ttacactgag ttctctaaaat ctggtataga ttttggctcc 780
cttttaaga aggataatga ggaaagtga caacctccag ttccaggaaac tcccacacta 840
aggaatcgta cttctcaga gtcttcgggt tgggtctcaac aatcttctag acctccttg 900
aaagatgggt ctctggagag ccaagataca gagaatgtcc cagttacact atcagaggag 960
aaccgttctg aaggaaaagt tgggttttcag gcctataaga attacttcag agctgggtgct 1020
cactggattg tcttcatttt ctttattctc gagcaccacc accaccacca ctga 1074

```

&lt;210&gt; 682

&lt;211&gt; 224

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 682

```

Met His His His His His Thr Ala Ala Ser Asp Asn Phe Gln Leu
      5                      10                      15

```

```

Ser Gln Gly Gly Gln Gly Phe Ala Ile Pro Ile Gly Gln Ala Met Ala

```

20	25	30
Ile Ala Gly Gln Ile Lys Leu Pro Thr Val His Ile Gly Pro Thr Ala		
35	40	45
Phe Leu Gly Leu Gly Val Val Asp Asn Asn Gly Asn Gly Ala Arg Val		
50	55	60
Gln Arg Val Val Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr		
65	70	75
Gly Asp Val Ile Thr Ala Val Asp Gly Ala Pro Ile Asn Ser Ala Thr		
85	90	95
Ala Met Ala Asp Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser		
100	105	110
Val Thr Trp Gln Thr Lys Ser Gly Gly Thr Arg Thr Gly Asn Val Thr		
115	120	125
Leu Ala Glu Gly Pro Pro Ala Glu Phe Met Ile Arg Glu Lys Phe Ala		
130	135	140
His Cys Thr Val Leu Thr Ile Ala His Arg Leu Asn Thr Ile Ile Asp		
145	150	155
Ser Asp Lys Ile Met Val Leu Asp Ser Gly Arg Leu Lys Glu Tyr Asp		
165	170	175
Glu Pro Tyr Val Leu Leu Gln Asn Lys Glu Ser Leu Phe Tyr Lys Met		
180	185	190
Val Gln Gln Leu Gly Lys Ala Glu Ala Ala Ala Leu Thr Glu Thr Ala		
195	200	205
Lys Gln Arg Trp Gly Phe Thr Met Leu Ala Arg Leu Val Ser Asn Ser		
210	215	220

&lt;210&gt; 683

&lt;211&gt; 357

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 683

Met Ser Ala Ile Glu Arg Val Ser Glu Ala Ile Val Ser Ile Arg Arg		
5	10	15

Ile Gln Thr Phe Leu Leu Leu Asp Glu Ile Ser Gln Arg Asn Arg Gln		
20	25	30

Leu Pro Ser Asp Gly Lys Lys Met Val His Val Gln Asp Phe Thr Ala		
35	40	45

Phe Trp Asp Lys Ala Ser Glu Thr Pro Thr Leu Gln Gly Leu Ser Phe

270

50	55	60
Thr Val Arg Pro Gly Glu Leu Leu Ala Val Val Gly Pro Val Gly Ala		
65	70	75 80
Gly Lys Ser Ser Leu Leu Ser Ala Val Leu Gly Glu Leu Ala Pro Ser		
	85	90 95
His Gly Leu Val Ser Val His Gly Arg Ile Ala Tyr Val Ser Gln Gln		
	100	105 110
Pro Trp Val Phe Ser Gly Thr Leu Arg Ser Asn Ile Leu Phe Gly Lys		
	115	120 125
Lys Tyr Glu Lys Glu Arg Tyr Glu Lys Val Ile Lys Ala Cys Ala Leu		
	130	135 140
Lys Lys Asp Leu Gln Leu Leu Glu Asp Gly Asp Leu Thr Val Ile Gly		
	145	150 155 160
Asp Arg Gly Thr Thr Leu Ser Gly Gly Gln Lys Ala Arg Val Asn Leu		
	165	170 175
Ala Arg Ala Val Tyr Gln Asp Ala Asp Ile Tyr Leu Leu Asp Asp Pro		
	180	185 190
Leu Ser Ala Val Asp Ala Glu Val Ser Arg His Leu Phe Glu Leu Cys		
	195	200 205
Ile Cys Gln Ile Leu His Glu Lys Ile Thr Ile Leu Val Thr His Gln		
	210	215 220
Leu Gln Tyr Leu Lys Ala Ala Ser Gln Ile Leu Ile Leu Lys Asp Gly		
	225	230 235 240
Lys Met Val Gln Lys Gly Thr Tyr Thr Glu Phe Leu Lys Ser Gly Ile		
	245	250 255
Asp Phe Gly Ser Leu Leu Lys Lys Asp Asn Glu Glu Ser Glu Gln Pro		
	260	265 270
Pro Val Pro Gly Thr Pro Thr Leu Arg Asn Arg Thr Phe Ser Glu Ser		
	275	280 285
Ser Val Trp Ser Gln Gln Ser Ser Arg Pro Ser Leu Lys Asp Gly Ala		
	290	295 300
Leu Glu Ser Gln Asp Thr Glu Asn Val Pro Val Thr Leu Ser Glu Glu		
	305	310 315 320
Asn Arg Ser Glu Gly Lys Val Gly Phe Gln Ala Tyr Lys Asn Tyr Phe		
	325	330 335
Arg Ala Gly Ala His Trp Ile Val Phe Ile Phe Leu Ile Leu Glu His		
	340	345 350
His His His His His		
	355	

<210> 684  
<211> 96  
<212> PRT  
<213> Homo sapiens

<400> 684  
Met Gly Ile Arg Glu Lys Phe Ala His Cys Thr Val Leu Thr Ile Ala  
                  5                  10                  15  
His Arg Leu Asn Thr Ile Ile Asp Ser Asp Lys Ile Met Val Leu Asp  
          20                  25                  30  
Ser Gly Arg Leu Lys Glu Tyr Asp Glu Pro Tyr Val Leu Leu Gln Asn  
          35                  40                  45  
Lys Glu Ser Leu Phe Tyr Lys Met Val Gln Gln Leu Gly Lys Ala Glu  
          50                  55                  60  
Ala Ala Ala Leu Thr Glu Thr Ala Lys Gln Arg Trp Gly Phe Thr Met  
          65                  70                  75                  80  
Leu Ala Arg Leu Val Ser Asn Ser Leu Glu His His His His His His  
                  85                  90                  95

<210> 685  
<211> 35  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> PCR primer

<400> 685  
cgcccatggg gatccgggag aaatttgccc actgc 35

<210> 686  
<211> 35  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> PCR primer

<400> 686  
cgcctcgagg gagtttgaga ccagcctggc caaca 35

<210> 687  
<211> 38  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> PCR primer

&lt;400&gt; 687

gcatggacca tatgtcagcc attgagaggg tgtcagag

38

&lt;210&gt; 688

&lt;211&gt; 34

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; PCR primer

&lt;400&gt; 688

ccgctcgaga ataaggaaaa tgaagacaat ccag

34

&lt;210&gt; 689

&lt;211&gt; 27

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; PCR primer

&lt;400&gt; 689

gttgaattca tgcacgggcc ccaggtg

27

&lt;210&gt; 690

&lt;211&gt; 30

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; PCR primer

&lt;400&gt; 690

cccctcgagt cactatgggc tgcctcttga

30

&lt;210&gt; 691

&lt;211&gt; 915

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 691

atgcatcacc atcaccatca cacggccgag tccgataact tccagctgtc ccagggtggg 60  
cagggtattcg ccattccgat cgggcaggcg atggcgatcg cgggccagat caagcttccc 120  
accgttcata tcgggcctac cgccttcctc ggcttgggtg ttgtcgacaa caacggcaac 180  
ggcgacagag tccaacgcgt ggtcgggagc gctccggcgg caagtctcgg catctccacc 240  
ggcgacgtga tcaccgcgtt cgacggcgct ccgatcaact cggccaccgc gatggcggac 300  
gcgcttaacg ggcacatccc cggtgacgtc atctcggtga cctggcaaac caagtcgggc 360  
ggcacgcgta cagggaacgt gacattggcc gagggacccc cggccgaatt catgcacggg 420  
ccccagggtc tggcacgctg ctccgagtgt gcttgcctg ccttggctgc cacctctgag 480  
ggggtgcgtc tggagggggt ggaccggcca ccaaccttac ccagtcaagg aagtggatgg 540  
ccatgttccc acagcctgag tggtgcccac ctgatggctg atggagcaaa ggccttagga 600  
aaagcagatg gcccttggcc ctacctttt gttagaagaa ctgatgttcc atgtcctgca 660  
gcgagtgagg ttggtggctg tgccccagc tcctggcggc ccctcgacaga ggtgactggt 720

```
<210> 692
<211> 304
<212> PRT
<213> Homo sapiens
```

<400> 692																
Met	His	His	His	His	His	His	Thr	Ala	Ala	Ser	Asp	Asn	Phe	Gln	Leu	
			5						10					15		
Ser	Gln	Gly	Gly	Gln	Gly	Phe	Ala	Ile	Pro	Ile	Gly	Gln	Ala	Met	Ala	
		20						25					30			
Ile	Ala	Gly	Gln	Ile	Lys	Leu	Pro	Thr	Val	His	Ile	Gly	Pro	Thr	Ala	
		35					40					45				
Phe	Leu	Gly	Leu	Gly	Val	Val	Asp	Asn	Asn	Gly	Asn	Gly	Ala	Arg	Val	
	50					55					60					
Gln	Arg	Val	Val	Gly	Ser	Ala	Pro	Ala	Ala	Ser	Leu	Gly	Ile	Ser	Thr	
65					70					75					80	
Gly	Asp	Val	Ile	Thr	Ala	Val	Asp	Gly	Ala	Pro	Ile	Asn	Ser	Ala	Thr	
			85						90					95		
Ala	Met	Ala	Asp	Ala	Leu	Asn	Gly	His	His	Pro	Gly	Asp	Val	Ile	Ser	
			100					105					110			
Val	Thr	Trp	Gln	Thr	Lys	Ser	Gly	Gly	Thr	Arg	Thr	Gly	Asn	Val	Thr	
		115					120					125				
Leu	Ala	Glu	Gly	Pro	Pro	Ala	Glu	Phe	Met	His	Gly	Pro	Gln	Val	Leu	
	130					135					140					
Ala	Arg	Cys	Ser	Glu	Cys	Ala	Cys	Pro	Ala	Leu	Ala	Ala	Thr	Ser	Ala	
145					150					155					160	
Gly	Val	Arg	Leu	Glu	Gly	Val	Asp	Arg	Pro	Pro	Thr	Leu	Pro	Ser	Gln	
				165					170					175		
Gly	Ser	Gly	Trp	Pro	Cys	Ser	His	Ser	Leu	Ser	Gly	Cys	His	Leu	Met	
			180					185					190			
Ala	Asp	Gly	Ala	Lys	Ala	Leu	Gly	Lys	Ala	Asp	Gly	Pro	Trp	Pro	Tyr	
		195					200					205				
Leu	Phe	Val	Arg	Arg	Thr	Asp	Val	Pro	Cys	Pro	Ala	Ala	Ser	Glu	Val	
	210					215					220					
Gly	Gly	Cys	Ala	Pro	Ser	Ser	Trp	Arg	Ala	Leu	Ala	Glu	Val	Thr	Gly	
225					230					235					240	
Cys	Ser	Leu	Gly	Pro	Leu	Gly	Leu	Ala	Gln	His	Ala	Gln	Ala	Ser	Val	
				245					250					255		

274

Leu Leu Leu Cys Tyr Lys Trp Ser His Ile Gly Glu Thr Ser Ser His  
 260 265 270

Leu Arg Ser Lys Val Tyr Ala Ala Phe Gly Gly Ser Ser Pro Cys Leu  
 275 280 285

Lys Gly Leu Met Ser Leu Trp Ala Ser Trp Leu Ser Arg Gly Arg Pro  
 290 295 300

<210> 693  
 <211> 24  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> PCR primer

<400> 693  
 cgaagtcacg tggaggccag cctc

24

<210> 694  
 <211> 29  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> PCR primer

<400> 694  
 cctgaccgaa ttcattaact ggcctggac

29

<210> 695  
 <211> 166  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> VARIANT  
 <222> (1)...(166)  
 <223> Xaa = Any Amino Acid

<400> 695  
 Met Gly His His His His His Val Glu Ala Ser Leu Ser Val Arg  
 1 5 10 15  
 His Pro Glu Tyr Asn Arg Pro Leu Leu Ala Asn Asp Leu Met Leu Ile  
 20 25 30  
 Lys Leu Asp Glu Ser Val Ser Glu Ser Asp Thr Ile Arg Ser Ile Ser  
 35 40 45  
 Ile Ala Ser Gln Cys Pro Thr Ala Gly Asn Ser Cys Leu Val Ser Gly  
 50 55 60  
 Trp Gly Leu Leu Ala Asn Gly Arg Met Pro Thr Val Leu Gln Cys Val  
 65 70 75 80  
 Asn Val Ser Val Val Ser Glu Glu Val Cys Ser Lys Leu Tyr Asp Pro

```
<210> 696
<211> 504
<212> DNA
<213> Homo sapiens
```

```
<220>
<221> misc_feature
<222> (1)...(504)
<223> n = A,T,C or G
```

<400>	696						
atgggccatc	atcatcatca	tcaogtggag	gccagcctct	ccgtacggca	cccagagtac		60
aacagaccct	tgtctgctaa	cgacctcatg	ctcatcaagt	tggacgaatc	cgtgtccgag		120
tctgacacca	tccggagcat	cagcattgct	tgcagtgcc	ctaccgcggg	gaactcttgc		180
ctcgtttctg	gctggggctct	gctggcgaac	ggcagaatgc	ctaccgtgct	gcagtgcgtg		240
aacgtgtcgg	tggtgtctga	ggaggtctgc	agtaagctct	atgaccgcgt	gtaccacccc		300
agcatgttct	gcgcgggcgg	agggcaanac	cagaangact	octgcaacgg	tgactctggg		360
gggccccttg	tctgccaacg	gtacttgcag	ggccttgtgt	ctttcggaag	agccccgtgt		420
ggccaagtga	gcgtgcacgg	tgtctacacc	aacctctgca	aattcactga	gtggatagag		480
aaaaccctcc	agqccagtta	atga					504

```
<210> 697
<211> 21
<212> DNA
<213> Artificial Sequence
```

<220>  
<223> PCR primer

<400> 697  
ctcagggttc cggagccgcg g 21

```
<210> 698
<211> 35
<212> DNA
<213> Artificial Sequence
```

<220>  
<223> PCR primer

<400> 698  
ctatagaatt cattaccaa aagctgggct ccagc 35

<210> 699



<211> 241  
 <212> PRT  
 <213> Homo sapiens

<400> 699

Met	Gln	His	His	His	His	His	His	Leu	Arg	Val	Pro	Glu	Pro	Arg	Pro
1			5						10					15	
Gly	Glu	Ala	Lys	Ala	Glu	Gly	Ala	Ala	Pro	Pro	Thr	Pro	Ser	Lys	Pro
		20						25					30		
Leu	Thr	Ser	Phe	Leu	Ile	Gln	Asp	Ile	Leu	Arg	Asp	Gly	Ala	Gln	Arg
	35					40						45			
Gln	Gly	Gly	Arg	Thr	Ser	Ser	Gln	Arg	Gln	Arg	Asp	Pro	Glu	Pro	Glu
	50					55					60				
Pro	Glu	Pro	Glu	Pro	Glu	Gly	Gly	Arg	Ser	Arg	Ala	Gly	Ala	Gln	Asn
65					70				75						80
Asp	Gln	Leu	Ser	Thr	Gly	Pro	Arg	Ala	Ala	Pro	Glu	Glu	Ala	Glu	Thr
				85				90						95	
Leu	Ala	Glu	Thr	Glu	Pro	Glu	Arg	His	Leu	Gly	Ser	Tyr	Leu	Leu	Asp
		100						105					110		
Ser	Glu	Asn	Thr	Ser	Gly	Ala	Leu	Pro	Arg	Leu	Pro	Gln	Thr	Pro	Lys
	115						120					125			
Gln	Pro	Gln	Lys	Arg	Ser	Arg	Ala	Ala	Phe	Ser	His	Thr	Gln	Val	Ile
	130					135						140			
Glu	Leu	Glu	Arg	Lys	Phe	Ser	His	Gln	Lys	Tyr	Leu	Ser	Ala	Pro	Glu
145					150					155					160
Arg	Ala	His	Leu	Ala	Lys	Asn	Leu	Lys	Leu	Thr	Glu	Thr	Gln	Val	Lys
			165						170					175	
Ile	Trp	Phe	Gln	Asn	Arg	Arg	Tyr	Lys	Thr	Lys	Arg	Lys	Gln	Leu	Ser
		180					185						190		
Ser	Glu	Leu	Gly	Asp	Leu	Glu	Lys	His	Ser	Ser	Leu	Pro	Ala	Leu	Lys
	195						200					205			
Glu	Glu	Ala	Phe	Ser	Arg	Ala	Ser	Leu	Val	Ser	Val	Tyr	Asn	Ser	Tyr
	210					215					220				
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225					230					235					240
Trp															

<210> 700  
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 <212> DNA  
 <213> Homo sapiens

<400> 700

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ccaaggcttc	cccaaacc	taagcagccg	cagaagcgct	cccgagctgc	cttctccac	420
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cgggccacc	tggccaagaa	cctcaagctc	acggagaccc	aagtgaagat	atggttccag	540
aacagacgct	ataagactaa	gcgaaagcag	ctctcctcgg	agctgggaga	cttgagaaag	600
cactcctttt	tgccggccct	gaaagaggag	gccttctccc	gggcctccct	ggtctccgtg	660
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tggtaatga						729

277

<210> 701  
 <211> 27  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> PCR primer

<400> 701  
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27

<210> 702  
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<400> 702  
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33

<210> 703  
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 Leu Thr Trp Ala Thr Gly Gly His Cys Phe Ser Ser Glu Glu Ser Gly  
 35 40 45  
 Ala Val Asp Gly Ala Gly Gln Lys Lys Asp Arg Ala Trp Leu Arg Cys  
 50 55 60  
 Pro Glu Ala Val Ala Gly Phe Pro Leu Gly Ser Asp Cys Arg Glu Gly  
 65 70 75 80  
 Gly Arg Gln Gly Cys Gly Gly Ser Asp Asp Glu Asp Asp Leu Gly Val  
 85 90 95  
 Ala Pro Gly Leu Ala Pro Ala Trp Ala Leu Thr Gln Pro Pro Ser Gln  
 100 105 110  
 Ser Pro Gly Pro Gln Ser Leu Pro Ser Thr Pro Ser Ser Ile Trp Pro  
 115 120 125  
 Gln Trp Val Ile Leu Ile Thr Glu Leu Thr Ile Pro Ser Pro Ala His  
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 Gly Pro Pro Trp Leu Pro Asn Ala Leu Glu Arg Gly His Leu Val Arg  
 145 150 155 160  
 Glu

<210> 704  
 <211> 489  
 <212> DNA  
 <213> Homo sapiens

278

&lt;400&gt; 704

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gagtagtga						489

&lt;210&gt; 705

&lt;211&gt; 132

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 705

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Ala	Ile	Pro	Ile	Gly	Gln	Ala	Met	Ala	Ile	Ala	Gly	Gln	Ile	Arg	Ser
		20						25					30		
Gly	Gly	Gly	Ser	Pro	Thr	Val	His	Ile	Gly	Pro	Thr	Ala	Phe	Leu	Gly
		35					40					45			
Leu	Gly	Val	Val	Asp	Asn	Asn	Gly	Asn	Gly	Ala	Arg	Val	Gln	Arg	Val
	50				55					60					
Val	Gly	Ser	Ala	Pro	Ala	Ala	Ser	Leu	Gly	Ile	Ser	Thr	Gly	Asp	Val
65					70					75				80	
Ile	Thr	Ala	Val	Asp	Gly	Ala	Pro	Ile	Asn	Ser	Ala	Thr	Ala	Met	Ala
				85					90					95	
Asp	Ala	Leu	Asn	Gly	His	His	Pro	Gly	Asp	Val	Ile	Ser	Val	Asn	Trp
			100					105						110	
Gln	Thr	Lys	Ser	Gly	Gly	Thr	Arg	Thr	Gly	Asn	Val	Thr	Leu	Ala	Glu
			115				120						125		
Gly	Pro	Pro	Ala												
			130												

&lt;210&gt; 706

&lt;211&gt; 31

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; PCR primer

&lt;400&gt; 706

ggggaattca tcacctatgt gccgcctctg c

31

&lt;210&gt; 707

&lt;211&gt; 40

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; PCR primer

279

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40

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<213> Homo sapiens

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accgttcata tcgggcctac cgccttcctc ggcttgggtg ttgtcgacaa caacggcaac 180  
ggcgacgag tccaacgcgt ggtcgggagc gctccggcgg caagtctcgg catctccacc 240  
ggcgacgtga tcaccgcggt cgacggcgct ccgatcaact cggccaccgc gatggcggac 300  
gcgtttaacg ggcacatcc cgtgacgtc atctcgggtga cctggcaaac caagtccggc 360  
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cgtggacgct atggccgcgg ccggcccttc atctgggcac tgccttggg catcctgctg 600  
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tga 1203

<210> 709  
<211> 400  
<212> PRT  
<213> Homo sapiens

<400> 709  
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Ile Ala Gly Gln Ile Lys Leu Pro Thr Val His Ile Gly Pro Thr Ala  
35 40 45  
Phe Leu Gly Leu Gly Val Val Asp Asn Asn Gly Asn Gly Ala Arg Val  
50 55 60  
Gln Arg Val Val Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr  
65 70 75 80  
Gly Asp Val Ile Thr Ala Val Asp Gly Ala Pro Ile Asn Ser Ala Thr  
85 90 95  
Ala Met Ala Asp Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser

280

100	105	110
Val Thr Trp Gln Thr Lys Ser Gly Gly Thr Arg Thr Gly Asn Val Thr		
115	120	125
Leu Ala Glu Gly Pro Pro Ala Glu Phe Ile Thr Tyr Val Pro Pro Leu		
130	135	140
Leu Leu Glu Val Gly Val Glu Glu Lys Phe Met Thr Met Val Leu Gly		
145	150	155
Ile Gly Pro Val Leu Gly Leu Val Cys Val Pro Leu Leu Gly Ser Ala		
165	170	175
Ser Asp His Trp Arg Gly Arg Tyr Gly Arg Arg Arg Pro Phe Ile Trp		
180	185	190
Ala Leu Ser Leu Gly Ile Leu Leu Ser Leu Phe Leu Ile Pro Arg Ala		
195	200	205
Gly Trp Leu Ala Gly Leu Leu Cys Pro Asp Pro Arg Pro Leu Glu Leu		
210	215	220
Ala Leu Leu Ile Leu Gly Val Gly Leu Leu Asp Phe Cys Gly Gln Val		
225	230	235
Cys Phe Thr Pro Leu Glu Ala Leu Leu Ser Asp Leu Phe Arg Asp Pro		
245	250	255
Asp His Cys Arg Gln Ala Tyr Ser Val Tyr Ala Phe Met Ile Ser Leu		
260	265	270
Gly Gly Cys Leu Gly Tyr Leu Leu Pro Ala Ile Asp Trp Asp Thr Ser		
275	280	285
Ala Leu Ala Pro Tyr Leu Gly Thr Gln Glu Glu Cys Leu Phe Gly Leu		
290	295	300
Leu Thr Leu Ile Phe Leu Thr Cys Val Ala Ala Thr Leu Leu Val Ala		
305	310	315
Glu Glu Ala Ala Leu Gly Pro Thr Glu Pro Ala Glu Gly Leu Ser Ala		
325	330	335
Pro Ser Leu Ser Pro His Cys Cys Pro Cys Arg Ala Arg Leu Ala Phe		
340	345	350
Arg Asn Leu Gly Ala Leu Leu Pro Arg Leu His Gln Leu Cys Cys Arg		
355	360	365
Met Pro Arg Thr Leu Arg Arg Leu Phe Val Ala Glu Leu Cys Ser Trp		
370	375	380
Met Ala Leu Met Thr Phe Thr Leu Phe Tyr Thr Asp Phe Val Gly Glu		
385	390	395
		400

281

<210> 710  
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<212> PRT  
<213> Homo sapiens

<400> 710  
Leu Leu Pro Pro Pro Ala Leu Cys Gly Ala Ser Ala Cys Asp Val  
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Ser Val Arg Val  
                  20

<210> 711  
<211> 60  
<212> DNA  
<213> Homo sapiens

<400> 711  
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<210> 712  
<211> 10  
<212> PRT  
<213> Homo sapiens

<400> 712  
Ala Ser Ala Cys Asp Val Ser Val Arg Val  
                  5                  10

<210> 713  
<211> 30  
<212> DNA  
<213> Homo sapiens

<400> 713  
gcctctgcct gtgatgtctc cgtacgtgtg 30

<210> 714  
<211> 9  
<212> PRT  
<213> Homo sapiens

<400> 714  
Ala Ser Ala Cys Asp Val Ser Val Arg  
  1                  5

<210> 715  
<211> 9  
<212> PRT  
<213> Homo sapiens

<400> 715  
Ser Ala Cys Asp Val Ser Val Arg Val  
                  5

<210> 716  
<211> 27

282

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 716

tctgcctgtg atgtctccgt acgtgtg

27

&lt;210&gt; 717

&lt;211&gt; 19

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 717

Gly Ile Gly Pro Val Leu Gly Leu Val Cys Val Pro Leu Leu Gly Ser  
5 10 15

Ala Ser Asp

&lt;210&gt; 718

&lt;211&gt; 19

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 718

Val Pro Pro Leu Leu Leu Glu Val Gly Val Glu Glu Lys Phe Met Thr  
5 10 15

Met Val Leu

&lt;210&gt; 719

&lt;211&gt; 19

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 719

Met Val Gln Arg Leu Trp Val Ser Arg Leu Leu Arg His Arg Lys Ala  
5 10 15

Gln Leu Leu

&lt;210&gt; 720

&lt;211&gt; 57

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;222&gt; (1)...(57)

&lt;223&gt; n = A,T,C or G

&lt;400&gt; 720

ggcnathggnc cngtnytnngg nytngtntgy gtnccnytny tnggnwsngc nwsngay 57

<210> 721  
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<212> DNA  
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<220>  
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<212> PRT  
<213> Homo sapiens

<400> 723  
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1 5

<210> 724  
<211> 9  
<212> PRT  
<213> Homo sapiens

<400> 724  
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1 5

<210> 725  
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<212> PRT  
<213> Homo sapiens

<400> 725  
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1 5

<210> 726  
<211> 9  
<212> PRT



<213> Homo sapiens

<400> 726

Met Leu Ile Lys Leu Asp Glu Ser Val

1

5

<210> 727

<211> 9

<212> PRT

<213> Homo sapiens

<400> 727

Leu Leu Ala Asn Asp Leu Met Leu Ile

1

5

<210> 728

<211> 10

<212> PRT

<213> Homo sapiens

<400> 728

Leu Leu Ala Asn Gly Arg Met Pro Thr Val

1

5

10

<210> 729

<211> 10

<212> PRT

<213> Homo sapiens

<400> 729

Leu Met Leu Ile Lys Leu Asp Glu Ser Val

1

5

10

<210> 730

<211> 10

<212> PRT

<213> Homo sapiens

<400> 730

Val Leu Gln Cys Val Asn Val Ser Val Val

1

5

10

<210> 731

<211> 10

<212> PRT

<213> Homo sapiens

<400> 731

Gly Leu Leu Ala Asn Gly Arg Met Pro Thr

1

5

10

<210> 732

<211> 10

<212> PRT

<213> Homo sapiens

<400> 732

Thr Val Leu Gln Cys Val Asn Val Ser Val

285

1 5 10

&lt;210&gt; 733

&lt;211&gt; 9

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 733

Gly Val Leu Val His Pro Gln Trp Val

1

5

&lt;210&gt; 734

&lt;211&gt; 9

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 734

Val Leu Val His Pro Gln Trp Val Leu

1

5

&lt;210&gt; 735

&lt;211&gt; 1195

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 735

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&lt;210&gt; 736

&lt;211&gt; 339

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 736

Met Glu Ser Arg Lys Asp Ile Thr Asn Gln Glu Glu Leu Trp Lys Met

5

10

15

Lys Pro Arg Arg Asn Leu Glu Glu Asp Asp Tyr Leu His Lys Asp Thr  
 20 25 30  
 Gly Glu Thr Ser Met Leu Lys Arg Pro Val Leu Leu His Leu His Gln  
 35 40 45  
 Thr Ala His Ala Asp Glu Phe Asp Cys Pro Ser Glu Leu Gln His Thr  
 50 55 60  
 Gln Glu Leu Phe Pro Gln Trp His Leu Pro Ile Lys Ile Ala Ala Ile  
 65 70 75 80  
 Ile Ala Ser Leu Thr Phe Leu Tyr Thr Leu Leu Arg Glu Val Ile His  
 85 90 95  
 Pro Leu Ala Thr Ser His Gln Gln Tyr Phe Tyr Lys Ile Pro Ile Leu  
 100 105 110  
 Val Ile Asn Lys Val Leu Pro Met Val Ser Ile Thr Leu Leu Ala Leu  
 115 120 125  
 Val Tyr Leu Pro Gly Val Ile Ala Ala Ile Val Gln Leu His Asn Gly  
 130 135 140  
 Thr Lys Tyr Lys Lys Phe Pro His Trp Leu Asp Lys Trp Met Leu Thr  
 145 150 155 160  
 Arg Lys Gln Phe Gly Leu Leu Ser Phe Phe Phe Ala Val Leu His Ala  
 165 170 175  
 Ile Tyr Ser Leu Ser Tyr Pro Met Arg Arg Ser Tyr Arg Tyr Lys Leu  
 180 185 190  
 Leu Asn Trp Ala Tyr Gln Gln Val Gln Gln Asn Lys Glu Asp Ala Trp  
 195 200 205  
 Ile Glu His Asp Val Trp Arg Met Glu Ile Tyr Val Ser Leu Gly Ile  
 210 215 220  
 Val Gly Leu Ala Ile Leu Ala Leu Leu Ala Val Thr Ser Ile Pro Ser  
 225 230 235 240  
 Val Ser Asp Ser Leu Thr Trp Arg Glu Phe His Tyr Ile Gln Ser Lys  
 245 250 255  
 Leu Gly Ile Val Ser Leu Leu Leu Gly Thr Ile His Ala Leu Ile Phe  
 260 265 270  
 Ala Trp Asn Lys Trp Ile Asp Ile Lys Gln Phe Val Trp Tyr Thr Pro  
 275 280 285  
 Pro Thr Phe Met Ile Ala Val Phe Leu Pro Ile Val Val Leu Ile Phe  
 290 295 300  
 Lys Ser Ile Leu Phe Leu Pro Cys Leu Arg Lys Lys Ile Leu Lys Ile  
 305 310 315 320  
 Arg His Gly Trp Glu Asp Val Thr Lys Ile Asn Lys Thr Glu Ile Cys

325

330

335

Ser Gln Leu

&lt;210&gt; 737

&lt;211&gt; 2172

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 737

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ccatttttagt actatgggtg agtacatgga attgaagtct ggcttaaata ttcagaaagt 180
tatatatcta ttttatttta tttttttgag acagagtctc gctgtgtcac ccaggctgga 240
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tgcctcggcc tcctgagtag ctgggactac aggcgtgcac caccacatct ggctaattct 360
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&lt;210&gt; 738

&lt;211&gt; 2455

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 738

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&lt;210&gt; 739

&lt;211&gt; 2455

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 739

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&lt;210&gt; 740

&lt;211&gt; 62

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 740

```

Met Thr His Ser Ser Ala Trp Leu Glu Arg Pro Gln Glu Thr Tyr Asn
          5                      10                      15

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His Gly Gly Arg Arg Arg Gly Ser Lys Ala Arg Leu Thr Trp Trp Gln
      20                      25                      30

```

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Glu Arg Thr Ser Glu Gly Gly Asp Cys His Lys Leu Phe Phe Phe Glu
      35                      40                      45

```

```

Thr Arg Val Trp Pro Cys Cys Pro Gly Trp Ser Ala Val Ala
      50                      55                      60

```

&lt;210&gt; 741

&lt;211&gt; 135

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 741

```

Met Val Glu Gly Glu Gly Glu Ala Arg His Val Leu His Gly Gly Arg
          5                      10                      15

```

290

Arg Glu Arg Val Arg Gly Glu Thr Ala Thr Asn Phe Phe Phe Leu Arg  
                   20                                  25                                  30  
 Gln Glu Ser Gly Pro Val Ala Gln Ala Gly Val Gln Trp His Asp Leu  
                   35                                  40                                  45  
 Ser Ser Leu Gln Pro Leu Pro His Arg Phe Lys Gln Phe Ser Cys Leu  
                   50                                  55                                  60  
 Ser Leu Pro His Ser Trp Asp His Arg Tyr Ala Pro Pro His Leu Ala  
                   65                                  70                                  75                                  80  
 Asn Phe Cys Ser Phe Ser Arg Asp Gly Val Ser Leu Cys Cys Ser Gly  
                                   85                                  90                                  95  
 Trp Ser Lys Thr Pro Gly Leu Gln Gln Ser Ala Cys Leu Gly Leu Pro  
                   100                                  105                                  110  
 Lys Cys Trp Gly Tyr Arg His Lys Pro Pro His Pro Ala Cys His Ile  
                   115                                  120                                  125  
 Leu Leu Asn Tyr Gln Val Ser  
                   130                                  135

&lt;210&gt; 742

&lt;211&gt; 77

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 742

Met His Tyr His Lys Asn Ser Met Gly Lys Ile Pro Pro Ile Ile Gln  
                                   5                                  10                                  15  
 Ser Pro Pro Thr Arg Ser Pro Pro Thr Arg Gly Ile Gly Trp Gly His  
                   20                                  25                                  30  
 Arg Ala Lys Pro Tyr Gln Met Leu Gln Gly Leu Gly Thr Leu Arg Pro  
                   35                                  40                                  45  
 Leu Arg Pro Gly Val Ser Val Thr Leu Leu Gly Ser Val Cys Leu Gln  
                   50                                  55                                  60  
 Asp Leu Pro Pro Leu Pro Trp Tyr Arg Arg Lys Val Leu  
                   65                                  70                                  75

&lt;210&gt; 743

&lt;211&gt; 60

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 743

Met Leu Val His Ile Tyr Ser Cys Cys Gly Met Val Tyr Arg Phe Gly  
                                   5                                  10                                  15  
 Gln Met Ser Asp Asn Pro Phe Tyr Ile Leu Ala Ser Leu Gly Ser Ser  
                   20                                  25                                  30

Ser Cys Arg Asn Gly Leu Ala Ser Lys Trp Arg Gln Ala Asp Pro Ser  
           35                          40                          45

Asp Gly Tyr Met Glu Pro Cys Phe Gln Leu Leu Phe  
           50                          55                          60

<210> 744

<211> 76

<212> PRT

<213> Homo sapiens

<400> 744

Met Cys Leu Cys Ile Pro Leu Gly Gly Tyr Gln Glu Leu Cys His Cys  
                           5                          10                          15

Met Ser Thr Ser Asp Gly Phe Ala Pro Pro Pro Gln Leu Gly Ser Arg  
                           20                          25                          30

Cys Ser His Ile Arg Gly Pro Ile Lys Ile Ala Arg Asn Lys Phe Pro  
                           35                          40                          45

Arg Thr Leu Thr Ser Gln Glu Leu Arg Arg Phe Ala Glu Tyr Ser Gly  
                           50                          55                          60

Met Met Phe Gly Asp Gln Thr Thr Ala Gly Gln Lys  
           65                          70                          75

<210> 745

<211> 76

<212> PRT

<213> Homo sapiens

<400> 745

Met Val Lys Ser Arg Phe Thr Lys Asn Thr Lys Ile Thr Gln Ala Trp  
                           5                          10                          15

Trp Arg Ala Pro Val Ile Pro Gly Thr Arg Glu Ala Glu Gly Gly Glu  
                           20                          25                          30

Ser Leu Glu Pro Gly Arg Leu Arg Glu Glu Asn Arg Leu Asn Pro Gly  
                           35                          40                          45

Gly Arg Gly Cys Ser Glu Pro Arg Ser Cys Cys Cys Thr Pro Ala Trp  
                           50                          55                          60

Ser Thr Glu Gln Asp Ser Ala Ser Lys Thr Asn Lys  
           65                          70                          75

<210> 746

<211> 80

<212> PRT

<213> Homo sapiens

<400> 746

Met Leu Leu His Ser Ser Leu Val Asn Arg Ala Arg Leu Cys Leu Lys



				5				10				15			
Asn	Lys	Gln	Ile	Asn	Lys	Gln	Thr	Asn	Lys	Thr	Glu	Arg	Phe	Cys	Cys
20				25								30			
Asn	Val	Gln	Gly	Ala	Ile	Cys	Ser	Phe	Lys	Lys	Ile	Ile	Phe	Gly	Gln
35				40								45			
Ala	Gln	Trp	Leu	Thr	Pro	Val	Ile	Pro	Ala	Leu	Trp	Glu	Ala	Lys	Val
50				55								60			
Gly	Gly	Ser	Phe	Glu	Val	Arg	Ser	Leu	Arg	Ser	Ala	Trp	Pro	Thr	Trp
65				70								75			
												80			

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<210> 747
<211> 72
<212> PRT
<213> Homo sapiens
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<400> 747
Met His Tyr His Lys Asn Ser Met Gly Lys Ile Pro Pro His Asn Pro
          5                               10                      15

Ile Thr Ser His Gln Val Ser Ser Asp Thr Trp Asp Trp Val Gly Thr
          20                               25                      30

Gln Ser Gln Thr Val Ser Asp Ala Ala Gly Ala Gly Asp Thr Glu Thr
          35                               40                      45

Thr Gln Thr Trp Cys Leu Cys His Ser Ser Gly Leu Cys Leu Ser Pro
          50                               55                      60

Gly Pro Pro Ser Pro Ser Met Val
          65                               70

```

```
<210> 748
<211> 77
<212> PRT
<213> Homo sapiens
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<400> 748

Met His Tyr His Lys Asn Ser Met Gly Lys Ile Pro Pro Ile Ile Gln  
5 10 15

Ser Pro Pro Thr Arg Ser Pro Pro Thr Arg Gly Ile Gly Trp Gly His  
20 25 30

Arg Ala Lys Pro Tyr Gln Met Leu Gln Gly Leu Gly Thr Leu Arg Pro  
35 40 45

Leu Arg Pro Gly Val Ser Val Thr Leu Leu Gly Ser Val Cys Leu Gln  
50 55 60

Asp Leu Pro Pro Leu Pro Trp Tyr Arg Arg Lys Val Leu  
65 70 75

<210> 749  
 <211> 60  
 <212> PRT  
 <213> Homo sapiens

<400> 749  
 Met Leu Val His Ile Tyr Ser Cys Cys Gly Met Val Tyr Arg Phe Gly  
                   5                  10                  15  
 Gln Met Ser Asp Asn Pro Phe Tyr Ile Leu Ala Ser Leu Gly Ser Ser  
                   20                  25                  30  
 Ser Cys Arg Asn Gly Leu Ala Ser Lys Trp Arg Gln Ala Asp Pro Ser  
                   35                  40                  45  
 Asp Gly Tyr Met Glu Pro Cys Phe Gln Leu Leu Phe  
           50                  55                  60

<210> 750  
 <211> 76  
 <212> PRT  
 <213> Homo sapiens

<400> 750  
 Met Cys Leu Cys Ile Pro Leu Gly Gly Tyr Gln Glu Leu Cys His Cys  
                   5                  10                  15  
 Met Ser Thr Ser Asp Gly Phe Ala Pro Pro Pro Gln Leu Gly Ser Arg  
                   20                  25                  30  
 Cys Ser His Ile Arg Gly Pro Ile Lys Ile Ala Arg Asn Lys Phe Pro  
                   35                  40                  45  
 Arg Thr Leu Thr Ser Gln Glu Leu Arg Arg Phe Ala Glu Tyr Ser Gly  
           50                  55                  60  
 Met Met Phe Gly Asp Gln Thr Thr Ala Gly Gln Lys  
           65                  70                  75

<210> 751  
 <211> 2479  
 <212> DNA  
 <213> Homo sapiens

<400> 751  
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2479

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&lt;210&gt; 752

&lt;211&gt; 492

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 752

Met Ala Leu Asn Ser Gly Ser Pro Pro Ala Ile Gly Pro Tyr Tyr Glu  
5 10 15

Asn His Gly Tyr Gln Pro Glu Asn Pro Tyr Pro Ala Gln Pro Thr Val  
20 25 30

Val Pro Thr Val Tyr Glu Val His Pro Ala Gln Tyr Tyr Pro Ser Pro  
35 40 45

Val Pro Gln Tyr Ala Pro Arg Val Leu Thr Gln Ala Ser Asn Pro Val  
50 55 60

Val Cys Thr Gln Pro Lys Ser Pro Ser Gly Thr Val Cys Thr Ser Lys  
65 70 75 80

Thr Lys Lys Ala Leu Cys Ile Thr Leu Thr Leu Gly Thr Phe Leu Val  
85 90 95

Gly Ala Ala Leu Ala Ala Gly Leu Leu Trp Lys Phe Met Gly Ser Lys

100					105					110					
Cys	Ser	Asn	Ser	Gly	Ile	Glu	Cys	Asp	Ser	Ser	Gly	Thr	Cys	Ile	Asn
		115					120					125			
Pro	Ser	Asn	Trp	Cys	Asp	Gly	Val	Ser	His	Cys	Pro	Gly	Gly	Glu	Asp
		130				135					140				
Glu	Asn	Arg	Cys	Val	Arg	Leu	Tyr	Gly	Pro	Asn	Phe	Ile	Leu	Gln	Met
145					150					155					160
Tyr	Ser	Ser	Gln	Arg	Lys	Ser	Trp	His	Pro	Val	Cys	Gln	Asp	Asp	Trp
				165					170					175	
Asn	Glu	Asn	Tyr	Gly	Arg	Ala	Ala	Cys	Arg	Asp	Met	Gly	Tyr	Lys	Asn
			180					185					190		
Asn	Phe	Tyr	Ser	Ser	Gln	Gly	Ile	Val	Asp	Asp	Ser	Gly	Ser	Thr	Ser
		195					200					205			
Phe	Met	Lys	Leu	Asn	Thr	Ser	Ala	Gly	Asn	Val	Asp	Ile	Tyr	Lys	Lys
	210					215					220				
Leu	Tyr	His	Ser	Asp	Ala	Cys	Ser	Ser	Lys	Ala	Val	Val	Ser	Leu	Arg
225					230					235					240
Cys	Leu	Ala	Cys	Gly	Val	Asn	Leu	Asn	Ser	Ser	Arg	Gln	Ser	Arg	Ile
				245					250					255	
Val	Gly	Gly	Glu	Ser	Ala	Leu	Pro	Gly	Ala	Trp	Pro	Trp	Gln	Val	Ser
			260					265					270		
Leu	His	Val	Gln	Asn	Val	His	Val	Cys	Gly	Gly	Ser	Ile	Ile	Thr	Pro
		275					280					285			
Glu	Trp	Ile	Val	Thr	Ala	Ala	His	Cys	Val	Glu	Lys	Pro	Leu	Asn	Asn
	290					295					300				
Pro	Trp	His	Trp	Thr	Ala	Phe	Ala	Gly	Ile	Leu	Arg	Gln	Ser	Phe	Met
305					310					315					320
Phe	Tyr	Gly	Ala	Gly	Tyr	Gln	Val	Gln	Lys	Val	Ile	Ser	His	Pro	Asn
				325					330					335	
Tyr	Asp	Ser	Lys	Thr	Lys	Asn	Asn	Asp	Ile	Ala	Leu	Met	Lys	Leu	Gln
			340					345					350		
Lys	Pro	Leu	Thr	Phe	Asn	Asp	Leu	Val	Lys	Pro	Val	Cys	Leu	Pro	Asn
		355					360					365			
Pro	Gly	Met	Met	Leu	Gln	Pro	Glu	Gln	Leu	Cys	Trp	Ile	Ser	Gly	Trp
	370					375					380				
Gly	Ala	Thr	Glu	Glu	Lys	Gly	Lys	Thr	Ser	Glu	Val	Leu	Asn	Ala	Ala
385					390					395					400
Lys	Val	Leu	Leu	Ile	Glu	Thr	Gln	Arg	Cys	Asn	Ser	Arg	Tyr	Val	Tyr
				405					410					415	

Asp Asn Leu Ile Thr Pro Ala Met Ile Cys Ala Gly Phe Leu Gln Gly  
 420 425 430

Asn Val Asp Ser Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Thr Ser  
 435 440 445

Asn Asn Asn Ile Trp Trp Leu Ile Gly Asp Thr Ser Trp Gly Ser Gly  
 450 455 460

Cys Ala Lys Ala Tyr Arg Pro Gly Val Tyr Gly Asn Val Met Val Phe  
 465 470 475 480

Thr Asp Trp Ile Tyr Arg Gln Met Lys Ala Asn Gly  
 485 490

&lt;210&gt; 753

&lt;211&gt; 683

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 753

```

gtcatattga acattccaga tacctatcat tactcgatgc tgttgataac agcaagatgg 60
ctttgaactc agggtcacca ccagctattg gaccttacta tgaaaacat ggataccaac 120
cggaaaaccc ctatcccgca cagcccaactg tggccccac tgtctacgag gtgcatccgg 180
ctcagtacta cccgtcccc gtgccccagt acgccccgag ggtcctgacg caggcticca 240
accccgtcgt ctgcacgcag cccaaatccc catccgggac agtgtgcacc tcaaagacta 300
agaaagcaact gtgcatcacc ttgacctgg ggaccttct cgtgggagct gcgctggcgg 360
ctggcctact ctggaagttc atgggcagca agtgcctcaa ctctgggata gagtgcgact 420
cctcaggtac ctgcatcaac ccctctaact ggtgtgatgg cgtgtcacac tgccccggcg 480
gggaggacga gaatcggtgt gttcgctct acggaccaa cttcatcctt cagatgtact 540
catctcagag gaagtctgt caccctgtgt gccaaagcga ctggaacgag aactacgggc 600
ggcgggcctg caggacatg ggctataaga ataattttta ctctagccaa ggaatagtgg 660
atgacagcgg atccaccagc ttt                                     683

```

&lt;210&gt; 754

&lt;211&gt; 209

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 754

```

Met Ala Leu Asn Ser Gly Ser Pro Pro Ala Ile Gly Pro Tyr Tyr Glu
1      5      10      15
Asn His Gly Tyr Gln Pro Glu Asn Pro Tyr Pro Ala Gln Pro Thr Val
20     25     30
Val Pro Thr Val Tyr Glu Val His Pro Ala Gln Tyr Tyr Pro Ser Pro
35     40     45
Val Pro Gln Tyr Ala Pro Arg Val Leu Thr Gln Ala Ser Asn Pro Val
50     55     60
Val Cys Thr Gln Pro Lys Ser Pro Ser Gly Thr Val Cys Thr Ser Lys
65     70     75     80
Thr Lys Lys Ala Leu Cys Ile Thr Leu Thr Leu Gly Thr Phe Leu Val
85     90     95

```

297

Gly Ala Ala Leu Ala Ala Gly Leu Leu Trp Lys Phe Met Gly Ser Lys  
                   100                  105                  110  
 Cys Ser Asn Ser Gly Ile Glu Cys Asp Ser Ser Gly Thr Cys Ile Asn  
           115                  120                  125  
 Pro Ser Asn Trp Cys Asp Gly Val Ser His Cys Pro Gly Gly Glu Asp  
       130                  135                  140  
 Glu Asn Arg Cys Val Arg Leu Tyr Gly Pro Asn Phe Ile Leu Gln Met  
 145                  150                  155                  160  
 Tyr Ser Ser Gln Arg Lys Ser Trp His Pro Val Cys Gln Asp Asp Trp  
                   165                  170                  175  
 Asn Glu Asn Tyr Gly Arg Ala Ala Cys Arg Asp Met Gly Tyr Lys Asn  
           180                  185                  190  
 Asn Phe Tyr Ser Ser Gln Gly Ile Val Asp Asp Ser Gly Ser Thr Ser  
       195                  200                  205  
 Phe

<210> 755  
 <211> 27  
 <212> PRT  
 <213> Homo sapiens

<400> 755  
 Val Gly Glu Gly Leu Tyr Gln Gly Val Pro Arg Ala Glu Pro Gly Thr  
   1                  5                  10                  15  
 Glu Ala Arg Arg His Tyr Asp Glu Gly Val Arg  
           20                  25

<210> 756  
 <211> 35  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> PCR primer

<400> 756  
 ggatccgccg ccaccatgtc actttctagc ctgct

35

<210> 757  
 <211> 27  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> PCR primer

<400> 757  
 gtcgactcag ctggaccaca gccgcag

27

<210> 758  
 <211> 34  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> PCR primer

<400> 758  
ggatccgccc ccaccatggg ctgcaggctg ctct

34

<210> 759  
<211> 27  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> PCR primer

<400> 759  
gtcgactcag aaatcctttc tcttgac

27

<210> 760  
<211> 936  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...()  
<223> n = A,T,C or G

<400> 760  
atgggctgca ggctgntctg ctgtgcggtt ctctgtctcc tgggagcggg ccccatggaa 60  
acgggagtta cgcagacacc aagacacctg gtcattggaa tgacaaataa gaagtctttg 120  
aaatgtgaac aacatctggg tcataacgct atgtattggt acaagcaaag tgctaagaag 180  
ccactggagc tcatgtttgt ctacagtctt gaagaacggg ttgaaaaca cagtgtgcca 240  
agtcgttct cactgaatg ccccaacagc tctcacttat tccttcacct acacaccctg 300  
cagccagaag actcggccct gtatctctgc gccagcagcc aagaccggac aagcagctcc 360  
tacgagcagt acttcgggcc gggcaccagg ctacagggtc cagaggacct gaaaaacgtg 420  
ttcccaccgg aggtcgctgt gtttgagcca tcagaagcag agatctcca caccctaaaag 480  
gccacactgg tgtgcctggc cacaggcttc taccocgacc acgtggagct gagctggtgg 540  
gtgaatggga aggaggtgca cagtggggtc agcacagacc cgcagccctt caaggagcag 600  
cccgccctca atgactccag atactgcctg agcagccgcc tgagggtctc ggccaccttc 660  
tggcagaacc cccgcaacca cttccgctgt caagtccagt tctacgggct ctcgagaaat 720  
gacgagtgga cccaggatag ggccaaacct gtcacccaga tcgtcagcgc cgaggccttg 780  
ggtagagcag actgtggctt cactccgag tcttaccagc aaggggtcct gtctgccacc 840  
atcctctatg agatcttgct aggaaggcc acctgtatg ccgtgctggt cagtgccttc 900  
gtgctgatgg ccattggtcaa gagaaaggat ttctga 936

<210> 761  
<211> 834  
<212> DNA  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<222> (1)...()  
<223> n = A,T,C or G

<400> 761  
atgtcacttt ctacgctgct naagggtggtc acagcttcac tgtggctagg acctggcatt 60  
gccagaaga taactcaaac ccaaccagga atgttcgtgc aggaaaagga ggctgtgact 120  
ctggactgca catatgacac cagtgtatcaa agttatggtc tcttctggta caagcagccc 180

```

agcagtgggg aaatgatttt tcttatttat caggggtctt atgacgagca aaatgcaaca 240
gaaggctcgt actcattgaa tttccagaag gcaagaaaat ccgccaacct tgtcatctcc 300
gcttcacaac tgggggactc agcaatgtat ttctgtgcaa tgagagaggg cgcgggagga 360
ggaaacaaac tcacctttgg gacaggcact cagctaaaag tggaaactcaa tatccagaac 420
cctgaccctg ccgtgtacca gctgagagac tctaaatcca gtgacaagtc tgtctgccta 480
ttcaccgatt ttgattctca aacaaatgtg tcacaaagta aggattctga tgtgtatc 540
acagacaaaa ctgtgctaga catgaggtct atggacttca agagcaacag tgctgtggcc 600
tggagcaaca aatctgactt tgcattgtca aacgccttca acaacagcat tattccagaa 660
gacaccttct tccccagccc agaaagtcc tgtgatgtca agctgggtcga gaaaagcttt 720
gaaacagata cgaacctaaa ctttcaaac ctgtcagtga ttgggttccg aatcctcctc 780
ctgaaagtgg ccgggtttta tctgctcatg acgctgcggc tgtggtccag ctga 834

```

&lt;210&gt; 762

&lt;211&gt; 311

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; variant

&lt;222&gt; (1)...(311)

&lt;223&gt; Xaa = Any amino acid

&lt;400&gt; 762

```

Met Gly Cys Arg Leu Xaa Cys Cys Ala Val Leu Cys Leu Leu Gly Ala
      5                      10                      15

```

```

Val Pro Met Glu Thr Gly Val Thr Gln Thr Pro Arg His Leu Val Met
      20                      25                      30

```

```

Gly Met Thr Asn Lys Lys Ser Leu Lys Cys Glu Gln His Leu Gly His
      35                      40                      45

```

```

Asn Ala Met Tyr Trp Tyr Lys Gln Ser Ala Lys Lys Pro Leu Glu Leu
      50                      55                      60

```

```

Met Phe Val Tyr Ser Leu Glu Glu Arg Val Glu Asn Asn Ser Val Pro
      65                      70                      75                      80

```

```

Ser Arg Phe Ser Pro Glu Cys Pro Asn Ser Ser His Leu Phe Leu His
      85                      90                      95

```

```

Leu His Thr Leu Gln Pro Glu Asp Ser Ala Leu Tyr Leu Cys Ala Ser
     100                      105                      110

```

```

Ser Gln Asp Arg Thr Ser Ser Ser Tyr Glu Gln Tyr Phe Gly Pro Gly
     115                      120                      125

```

```

Thr Arg Leu Thr Val Thr Glu Asp Leu Lys Asn Val Phe Pro Pro Glu
     130                      135                      140

```

```

Val Ala Val Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys
     145                      150                      155                      160

```

```

Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Tyr Pro Asp His Val Glu
     165                      170                      175

```

```

Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr
     180                      185                      190

```



300

Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr  
 195 200 205  
 Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro  
 210 215 220  
 Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn  
 225 230 235 240  
 Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser  
 245 250 255  
 Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Glu Ser Tyr  
 260 265 270  
 Gln Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly  
 275 280 285  
 Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala  
 290 295 300  
 Met Val Lys Arg Lys Asp Phe  
 305 310

<210> 763  
 <211> 277  
 <212> PRT  
 <213> Homo sapiens

<400> 763  
 Met Ser Leu Ser Ser Leu Leu Lys Val Val Thr Ala Ser Leu Trp Leu  
 5 10 15  
 Gly Pro Gly Ile Ala Gln Lys Ile Thr Gln Thr Gln Pro Gly Met Phe  
 20 25 30  
 Val Gln Glu Lys Glu Ala Val Thr Leu Asp Cys Thr Tyr Asp Thr Ser  
 35 40 45  
 Asp Gln Ser Tyr Gly Leu Phe Trp Tyr Lys Gln Pro Ser Ser Gly Glu  
 50 55 60  
 Met Ile Phe Leu Ile Tyr Gln Gly Ser Tyr Asp Glu Gln Asn Ala Thr  
 65 70 75 80  
 Glu Gly Arg Tyr Ser Leu Asn Phe Gln Lys Ala Arg Lys Ser Ala Asn  
 85 90 95  
 Leu Val Ile Ser Ala Ser Gln Leu Gly Asp Ser Ala Met Tyr Phe Cys  
 100 105 110  
 Ala Met Arg Glu Gly Ala Gly Gly Asn Lys Leu Thr Phe Gly Thr  
 115 120 125  
 Gly Thr Gln Leu Lys Val Glu Leu Asn Ile Gln Asn Pro Asp Pro Ala  
 130 135 140

Val Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu  
145 150 155 160

Phe Thr Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser  
165 170 175

Asp Val Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp  
180 185 190

Phe Lys Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala  
195 200 205

Cys Ala Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe  
210 215 220

Pro Ser Pro Glu Ser Ser Cys Asp Val Lys Leu Val Glu Lys Ser Phe  
225 230 235 240

Glu Thr Asp Thr Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe  
245 250 255

Arg Ile Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu  
260 265 270

Arg Leu Trp Ser Ser  
275

<210> 764

<211> 1536

<212> DNA

<213> Homo sapiens

<400> 764

atgtacaacc tgttgctgtc ctacgacaga catggggacc acctgcagcc cctggacctc 60  
gtgcccatac accagggtct caccctttc aagctggctg gagtggaggg taacactgtg 120  
atgtttcagc acctgatgca gaagcggaag cacacccagt ggacgtatgg accactgacc 180  
tcgactctct atgacctcac agagatcgac tcctcagggg atgagcagtc cctgtgtgaa 240  
cttatcatca ccaccaagaa gcgggaggct cgccagatcc tggaccagac gccggtgaag 300  
gagctgggtga gcctcaagtg gaagcggtag gggcgccgt acttctgcat gctgggtgcc 360  
atatatctgc tgtacatcat ctgcttcacc atgtgctgca tctaccgccc cctcaagccc 420  
aggaccaata accgcacgag ccccgggac aacaccctct tacagcagaa gctacttcag 480  
gaagcctaca tgacccctaa ggacgatata cggctggctg gggagctggg gactgtcatt 540  
ggggctatca tcatcctgct ggtagagggt ccagacatct tcagaatggg ggtcactcgc 600  
ttctttggac agaccatcct tgggggcca ttccatgtcc tcatcatcac ctatgccttc 660  
atggtgctgg tgaccatggt gatgcggctc atcagtcca gcggggagggt ggtaccatg 720  
tcctttgcac tcgtgctggg ctggtgcaac gtcatgtact tcgcccaggg attccagatg 780  
ctaggccctc tcaccatcat gattcagaag atgatttttg gcgacctgat gcgattctgc 840  
tggctgatgg ctgtggtcat cctgggcttt gcttcagcct tctatatcat cttccagaca 900  
gaggaccccg aggagctagg ccacttctac gactaccca tggccctgtt cagcaccttc 960  
gagctgttcc ttaccatcat cgatggcca gccaaactaca acgtggacct gcccttcatt 1020  
tacagcatca cctatgctgc ctttgccatc atcgccacac tgctcatgct caacctcctc 1080  
attgccatga tgggcgacac tcaactggcg gtggcccatg agcgggatga gctgtggagg 1140  
gccagattg tggccaccac ggtgatgctg gagcggaagc tgccctcgctg cctgtggcct 1200  
cgctccggga tctgcggacg ggagtatggc ctgggagacc gctggttcct gcgggtggaa 1260  
gacaggcaag atctcaaccg gcagcggatc caacgctacg cacaggcctt ccacacccgg 1320  
ggctctgagg atttgacaa agactcagtg gaaaaactag agctgggctg tcccttcagc 1380

```
<210> 765
<211> 1533
<212> DNA
<213> Homo sapiens
```

<400>	765						
atgtacaacc	tgttgctgtc	ctacgacaga	catggggacc	acctgcagcc	cctggacctc	60	
gtgccaatc	accagggtct	cacccctttc	aagctggctg	gagtggaggg	taacactgtg	120	
atgtttcagc	acctgatgca	gaagcggaag	cacaccaggt	ggacgtatgg	accactgacc	180	
tgcactctct	atgacctcac	agagatcgac	tcctcagggg	atgagcagtc	cctgctggaa	240	
cttatcatca	ccaccaagaa	gcgggagggt	cgccagatcc	tggaccagac	gccgggtgaag	300	
gagctgggtg	gcctcaagtg	gaagcgttac	ggcgggccgt	accttcgtac	gctgggtgcc	360	
atatatctgc	tgtacatcat	ctgctttacc	atgtgtctga	ttaccgcccc	cctcaagccc	420	
aggaccaata	accgcacgag	cccccgggac	aacacctct	tacagcagaa	gctacttcaag	480	
gaagcctaca	tgacctctaa	ggacgatatc	cggctggctg	gggagctggg	gactgtcatt	540	
ggggctatca	tcatcctgct	ggtagagggt	ccagacatct	tcagaatggg	ggtcactcgc	600	
ttctttggac	agaccatcct	tggggggcca	ttccatgtcc	tcatcatcac	ctatgccttc	660	
atggtgctgg	tgaccatggg	gatgcggctc	atcagtgcca	gcggggaggt	ggtaccatg	720	
tcctttgcac	tcgtgctggg	ctggtgcaac	gtcatgtact	tcgcccgagg	attccagatg	780	
ctaggccctc	tcaccatcat	gattcagaag	atgatttttg	gcgacctgat	gcgattctgc	840	
tggctgatgg	ctgtgggtcat	cctgggcttt	gcttcagcct	tctatatcat	cttcacagaca	900	
gaggcccccg	aggagcttagg	ccacttctac	gactacccca	tggccctggt	cagcaccttc	960	
gagctgttcc	ttaccatcat	cgatggccca	gccaaactaca	acgtggacct	gcccttcatg	1020	
tacagcatca	cctatgctgc	ctttgccatc	atgccacac	tgctcatgct	caacctcctc	1080	
attgccatga	tgggcgacac	tcactggcga	gtggcccatg	agcgggatga	gctgtggagg	1140	
gccagattg	tggccaccac	ggtgatgctg	gagcggaagc	tgcctcgctg	cctgtggcct	1200	
cgctccggga	tctgcggacg	ggagtatggc	ctgggagacc	gctggttcct	gcgggtggaa	1260	
gacaggcaag	atctcaaccg	gcagcggatc	caacgctacg	cacaggcctt	ccacaccogg	1320	
ggctctggtg	at ttggacaa	agactcagtg	gaaaaactag	agctgggctg	tccttccagc	1380	
ccccacctgt	cccttctcat	gccctcagtg	tctogaagta	cctcccgacg	cagtgccaat	1440	
tgggaaagcg	ttcggcaagg	gacctgagg	agagacctgc	gtgggataat	caacaggggt	1500	
ctggaggacg	gggagagctg	ggaatatcag	atc			1533	

```
<210> 766
<211> 511
<212> PRT
<213> Homo sapiens
```

<400> 766  
Met Tyr Asn Leu Leu Ser Tyr Asp Arg His Gly Asp His Leu Gln  
                  5                       10                       15

Pro Leu Asp Leu Val Pro Asn His Gln Gly Leu Thr Pro Phe Lys Leu  
20 25 30

Ala Gly Val Glu Gly Asn Thr Val Met Phe Gln His Leu Met Gln Lys  
35 40 45

Arg Lys His Thr Gln Trp Thr Tyr Gly Pro Leu Thr Ser Thr Leu Tyr  
50 55 60

Asp Leu Thr Glu Ile Asp Ser Ser Gly Asp Glu Gln Ser Leu Leu Glu  
65 70 75 80



304

385                      390                      395                      400  
 Arg Ser Gly Ile Cys Gly Arg Glu Tyr Gly Leu Gly Asp Arg Trp Phe  
                                  405                      410                      415  
 Leu Arg Val Glu Asp Arg Gln Asp Leu Asn Arg Gln Arg Ile Gln Arg  
                                  420                      425                      430  
 Tyr Ala Gln Ala Phe His Thr Arg Gly Ser Glu Asp Leu Asp Lys Asp  
                                  435                      440                      445  
 Ser Val Glu Lys Leu Glu Leu Gly Cys Pro Phe Ser Pro His Leu Ser  
                                  450                      455                      460  
 Leu Pro Met Pro Ser Val Ser Arg Ser Thr Ser Arg Ser Ser Ala Asn  
                                  465                      470                      475                      480  
 Trp Glu Arg Leu Arg Gln Gly Thr Leu Arg Arg Asp Leu Arg Gly Ile  
                                  485                      490                      495  
 Ile Asn Arg Gly Leu Glu Asp Gly Glu Ser Trp Glu Tyr Gln Ile  
                                  500                      505                      510

&lt;210&gt; 767

&lt;211&gt; 134

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 767

Met Tyr Asn Leu Leu Leu Ser Tyr Asp Arg His Gly Asp His Leu Gln  
                                  5                      10                      15  
 Pro Leu Asp Leu Val Pro Asn His Gln Gly Leu Thr Pro Phe Lys Leu  
                                  20                      25                      30  
 Ala Gly Val Glu Gly Asn Thr Val Met Phe Gln His Leu Met Gln Lys  
                                  35                      40                      45  
 Arg Lys His Thr Gln Trp Thr Tyr Gly Pro Leu Thr Ser Thr Leu Tyr  
                                  50                      55                      60  
 Asp Leu Thr Glu Ile Asp Ser Ser Gly Asp Glu Gln Ser Leu Leu Glu  
                                  65                      70                      75                      80  
 Leu Ile Ile Thr Thr Lys Lys Arg Glu Ala Arg Gln Ile Leu Asp Gln  
                                  85                      90                      95  
 Thr Pro Val Lys Glu Leu Val Ser Leu Lys Trp Lys Arg Tyr Gly Arg  
                                  100                      105                      110  
 Pro Tyr Phe Cys Met Leu Gly Ala Ile Tyr Leu Leu Tyr Ile Ile Cys  
                                  115                      120                      125  
 Phe Thr Met Cys Cys Ile  
                                  130

<210> 768  
<211> 55  
<212> PRT  
<213> Homo sapiens

<400> 768  
Ala Tyr Arg Pro Leu Lys Pro Arg Thr Asn Asn Arg Thr Ser Pro Arg  
                  5                  10                  15  
  
Asp Asn Thr Leu Leu Gln Gln Lys Leu Leu Gln Glu Ala Tyr Met Thr  
          20                  25                  30  
  
Pro Lys Asp Asp Ile Arg Leu Val Gly Glu Leu Val Thr Val Ile Gly  
          35                  40                  45  
  
Ala Ile Ile Ile Leu Leu Val  
      50                  55

<210> 769  
<211> 39  
<212> PRT  
<213> Homo sapiens

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<212> PRT  
<213> Homo sapiens

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306

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 <213> Homo sapiens  
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<400> 773

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<400> 774

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&lt;210&gt; 775

&lt;211&gt; 957

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 775

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&lt;210&gt; 776

&lt;211&gt; 954

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 776

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<400> 777

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Pro Leu Cys Ser Leu Tyr Leu Ile Ala Val Leu Gly Asn Leu Thr Ile  
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Ile Tyr Ile Val Arg Thr Glu His Ser Leu His Glu Pro Met Tyr Ile  
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Phe Leu Cys Met Leu Ser Gly Ile Asp Ile Leu Ile Ser Thr Ser Ser  
65 70 75 80

Met Pro Lys Met Leu Ala Ile Phe Trp Phe Asn Ser Thr Thr Ile Gln  
85 90 95

Phe Asp Ala Cys Leu Leu Gln Met Phe Ala Ile His Ser Leu Ser Gly  
100 105 110

Met Glu Ser Thr Val Leu Leu Ala Met Ala Phe Asp Arg Tyr Val Ala  
115 120 125

Ile Cys His Pro Leu Arg His Ala Thr Val Leu Thr Leu Pro Arg Val  
130 135 140

Thr Lys Ile Gly Val Ala Ala Val Val Arg Gly Ala Ala Leu Met Ala  
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Pro Leu Pro Val Phe Ile Lys Gln Leu Pro Phe Cys Arg Ser Asn Ile  
165 170 175

Leu Ser His Ser Tyr Cys Leu His Gln Asp Val Met Lys Leu Ala Cys  
180 185 190

Asp Asp Ile Arg Val Asn Val Val Tyr Gly Leu Ile Val Ile Ile Ser  
195 200 205

Ala Ile Gly Leu Asp Ser Leu Leu Ile Ser Phe Ser Tyr Leu Leu Ile  
210 215 220

Leu Lys Thr Val Leu Gly Leu Thr Arg Glu Ala Gln Ala Lys Ala Phe  
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Gly Thr Cys Val Ser His Val Cys Ala Val Phe Ile Phe Tyr Val Pro  
245 250 255

310

Phe Ile Gly Leu Ser Met Val His Arg Phe Ser Lys Arg Arg Asp Ser  
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Pro Leu Pro Val Ile Leu Ala Asn Ile Tyr Leu Leu Val Pro Pro Val  
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Leu Asn Pro Ile Val Tyr Gly Val Lys Thr Lys Glu Ile Arg Gln Arg  
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Ile Leu Arg Leu Phe His Val Ala Thr His Ala Ser Glu Pro  
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&lt;210&gt; 778

&lt;211&gt; 28

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 778

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Leu Ile Gly Leu Pro Gly Leu Glu Glu Ala Gln Phe  
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&lt;210&gt; 779

&lt;211&gt; 9

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 779

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&lt;210&gt; 780

&lt;211&gt; 21

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 780

Lys Met Leu Ala Ile Phe Trp Phe Asn Ser Thr Thr Ile Gln Phe Asp  
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&lt;210&gt; 781

&lt;211&gt; 20

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 781

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Tyr Cys Leu His Gln Asp Val Met Lys Leu Ala Cys Asp Asp Ile Arg  
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 <212> DNA  
 <213> Homo sapiens

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&lt;210&gt; 789

&lt;211&gt; 492

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 789

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Met Ala Leu Asn Ser Gly Ser Pro Pro Ala Ile Gly Pro Tyr Tyr Glu
      5              10              15
Asn His Gly Tyr Gln Pro Glu Asn Pro Tyr Pro Ala Gln Pro Thr Val
      20              25              30
Val Pro Thr Val Tyr Glu Val His Pro Ala Gln Tyr Tyr Pro Ser Pro
      35              40              45
Val Pro Gln Tyr Ala Pro Arg Val Leu Thr Gln Ala Ser Asn Pro Val
      50              55              60
Val Cys Thr Gln Pro Lys Ser Pro Ser Gly Thr Val Cys Thr Ser Lys
      65              70              75              80
Thr Lys Lys Ala Leu Cys Ile Thr Leu Thr Leu Gly Thr Phe Leu Val
      85              90              95
Gly Ala Ala Leu Ala Ala Gly Leu Leu Trp Lys Phe Met Gly Ser Lys
      100             105             110
Cys Ser Asn Ser Gly Ile Glu Cys Asp Ser Ser Gly Thr Cys Ile Asn
      115             120             125
Pro Ser Asn Trp Cys Asp Gly Val Ser His Cys Pro Gly Gly Glu Asp
      130             135             140
Glu Asn Arg Cys Val Arg Leu Tyr Gly Ser Asn Phe Ile Leu Gln Val
      145             150             155             160
Tyr Ser Ser Gln Arg Lys Ser Trp His Pro Val Cys Gln Asp Asp Trp
      165             170             175
Asn Glu Asn Tyr Gly Arg Ala Ala Cys Arg Asp Met Gly Tyr Lys Asn
      180             185             190
Asn Phe Tyr Ser Ser Gln Gly Ile Val Asp Asp Ser Gly Ser Thr Ser
      195             200             205
Phe Met Lys Leu Asn Thr Ser Ala Gly Asn Val Asp Ile Tyr Lys Lys
      210             215             220
Leu Tyr His Ser Asp Ala Cys Ser Ser Lys Ala Val Val Ser Leu Arg
      225             230             235             240
Cys Ile Ala Cys Gly Val Asn Leu Asn Ser Ser Arg Gln Ser Arg Ile
      245             250             255
Val Gly Gly Glu Ser Ala Leu Pro Gly Ala Trp Pro Trp Gln Val Ser
      260             265             270
Leu His Val Gln Asn Val His Val Cys Gly Gly Ser Ile Ile Thr Pro
      275             280             285
Glu Trp Ile Val Thr Ala Ala His Cys Val Glu Lys Pro Leu Asn Asn
      290             295             300
Pro Trp His Trp Thr Ala Phe Ala Gly Ile Leu Arg Gln Ser Phe Met
      305             310             315             320
Phe Tyr Gly Ala Gly Tyr Gln Val Glu Lys Val Ile Ser His Pro Asn
      325             330             335
Tyr Asp Ser Lys Thr Lys Asn Asn Asp Ile Ala Leu Met Lys Leu Gln
      340             345             350

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<211> 100
<212> PRT
<213> Homo sapiens
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<210> 791
<211> 393
<212> PRT
<213> Homo sapiens
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<400> 791															
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				5					10					15	
Ser	Gly	Ile	Glu	Cys	Asp	Ser	Ser	Gly	Thr	Cys	Ile	Asn	Pro	Ser	Asn
			20					25					30		
Trp	Cys	Asp	Gly	Val	Ser	His	Cys	Pro	Gly	Gly	Glu	Asp	Glu	Asn	Arg
			35				40					45			
Cys	Val	Arg	Leu	Tyr	Gly	Ser	Asn	Phe	Ile	Leu	Gln	Val	Tyr	Ser	Ser
	50					55					60				
Gln	Arg	Lys	Ser	Trp	His	Pro	Val	Cys	Gln	Asp	Trp	Asn	Glu	Asn	
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<211> 595
<212> PRT
<213> Homo sapiens
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<400> 792

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Leu	Ala	Ala	Pro	Val	Asn	Thr	Thr	Thr	Glu	Asp	Glu	Thr	Ala	Gln	Ile
			20					25					30		
Pro	Ala	Glu	Ala	Val	Ile	Gly	Tyr	Ser	Asp	Leu	Glu	Gly	Asp	Phe	Asp
		35					40					45			
Val	Ala	Val	Leu	Pro	Phe	Ser	Asn	Ser	Thr	Asn	Asn	Gly	Leu	Leu	Phe
	50					55					60				
Ile	Asn	Thr	Thr	Ile	Ala	Ser	Ile	Ala	Ala	Lys	Glu	Glu	Gly	Val	Ser
65					70					75					80

Leu Glu Lys Arg Glu Ala Glu Ala Met Val Leu Gly Ile Gly Pro Val  
 85 90 95  
 Leu Gly Leu Val Cys Val Pro Leu Leu Gly Ser Ala Ser Asp His Trp  
 100 105 110  
 Arg Gly Arg Tyr Gly Arg Arg Arg Pro Phe Ile Trp Ala Leu Ser Leu  
 115 120 125  
 Gly Ile Leu Leu Ser Leu Phe Leu Ile Pro Arg Ala Gly Trp Leu Ala  
 130 135 140  
 Gly Leu Leu Cys Pro Asp Pro Arg Pro Leu Glu Leu Ala Leu Leu Ile  
 145 150 155 160  
 Leu Gly Val Gly Leu Leu Asp Phe Cys Gly Gln Val Cys Phe Thr Pro  
 165 170 175  
 Leu Glu Ala Leu Leu Ser Asp Leu Phe Arg Asp Pro Asp His Cys Arg  
 180 185 190  
 Gln Ala Tyr Ser Val Tyr Ala Phe Met Ile Ser Leu Gly Gly Cys Leu  
 195 200 205  
 Gly Tyr Leu Leu Pro Ala Ile Asp Trp Asp Thr Ser Ala Leu Ala Pro  
 210 215 220  
 Tyr Leu Gly Thr Gln Glu Cys Leu Phe Gly Leu Leu Thr Leu Ile  
 225 230 235 240  
 Phe Leu Thr Cys Val Ala Ala Thr Leu Leu Val Ala Glu Glu Ala Ala  
 245 250 255  
 Leu Gly Pro Thr Glu Pro Ala Glu Gly Leu Ser Ala Pro Ser Leu Ser  
 260 265 270  
 Pro His Cys Cys Pro Cys Arg Ala Arg Leu Ala Phe Arg Asn Leu Gly  
 275 280 285  
 Ala Leu Leu Pro Arg Leu His Gln Leu Cys Cys Arg Met Pro Arg Thr  
 290 295 300  
 Leu Arg Arg Leu Phe Val Ala Glu Leu Cys Ser Trp Met Ala Leu Met  
 305 310 315 320  
 Thr Phe Thr Leu Phe Tyr Thr Asp Phe Val Gly Glu Gly Leu Tyr Gln  
 325 330 335  
 Gly Val Pro Arg Ala Glu Pro Gly Thr Glu Ala Arg Arg His Tyr Asp  
 340 345 350  
 Glu Gly Val Arg Met Gly Ser Leu Gly Leu Phe Leu Gln Cys Ala Ile  
 355 360 365  
 Ser Leu Val Phe Ser Leu Val Met Asp Arg Leu Val Gln Arg Phe Gly  
 370 375 380  
 Thr Arg Ala Val Tyr Leu Ala Ser Val Ala Ala Phe Pro Val Ala Ala  
 385 390 395 400  
 Gly Ala Thr Cys Leu Ser His Ser Val Ala Val Val Thr Ala Ser Ala  
 405 410 415  
 Ala Leu Thr Gly Phe Thr Phe Ser Ala Leu Gln Ile Leu Pro Tyr Thr  
 420 425 430  
 Leu Ala Ser Leu Tyr His Arg Glu Lys Gln Val Phe Leu Pro Lys Tyr  
 435 440 445  
 Arg Gly Asp Thr Gly Gly Ala Ser Ser Glu Asp Ser Leu Met Thr Ser  
 450 455 460  
 Phe Leu Pro Gly Pro Lys Pro Gly Ala Pro Phe Pro Asn Gly His Val  
 465 470 475 480  
 Gly Ala Gly Gly Ser Gly Leu Leu Pro Pro Pro Pro Ala Leu Cys Gly  
 485 490 495  
 Ala Ser Ala Cys Asp Val Ser Val Arg Val Val Val Gly Glu Pro Thr  
 500 505 510  
 Glu Ala Arg Val Val Pro Gly Arg Gly Ile Cys Leu Asp Leu Ala Ile  
 515 520 525  
 Leu Asp Ser Ala Phe Leu Leu Ser Gln Val Ala Pro Ser Leu Phe Met  
 530 535 540

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